PROFILE BOOKLET

Life Sciences

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Oxford University Innovation Limited

Buxton Court, 3 West Way
Oxford OX2 0JB

www.innovation.ox.ac.uk

TABLE OF CONTENTS

INFLAMMATORY DISEASES **1**

11412 Oncostatin-M: a novel therapeutic target for inflammatory bowel disease 2
17118 Improved anti-TNF Antibodies 3

DATA MANAGEMENT TOOLS **4**

11339 The Rare UK Disease Study platform (RUDY) 5

DEVICES AND DIAGNOSTICS **6**

706 Sulphide sensor 7
957 Layered double hydroxides 8
2476 Saliva drug testing 9
2718 Real word arsenic detection 10
7895 Bacterial identification 11
12408 Metal-free Catalysts 12
12729 FieldSense – Next generation tactile feedback systems 13
13022 Growth prediction of abdominal aortic aneurysms 14
13067 A Microfluidic Sonication Device for the Production of Coated Microbubbles 15
13151 Smart mouth guard 16
13249 Nuclear quadrupole resonance sensors for safer wireless power 17
13953 Density-of-state based quantum sensitive sensor 18
14262 Magnetic microbubble-conjugation thrombin as a novel drug delivery system 19
14654 Automated detection of bacterial growth from a photograph of a 96 well plate 20
15739 Deep clustering for phenotyping complex disease 21
15740 Probabilistic clustering of signatures 22
15823 A novel algorithm for biologically inspired lighting solutions 23
15840 Patient flow management system for hospitals and emergency departments 24
16143/16372 Multifunctional device for focusing light through an optical component 25
16684 A new dual-channel needle for the extraction of oocytes during the IVF process 26
16879 Classification of electrocardiogram datasets 27
17132 An automated deep learning system for ECG classification 28
17993 T cell peptide epitopes for reagents in COVID-19 testing 29
17999 Optimising the performance of specificity of RT-LAMP based assays 30
18187 Portable imaging device for early detection of cardiovascular disease 31
18209 Federated meta-learning for healthcare applications 32
18210 Machine learning framework using physiological data 33
18918 Shaping Sounds: patient specific waveguide arrays for therapeutic ultrasound 34

GENOMICS **35**

10531/15179 PubMLST molecular typing database 36
14061 Chromopainter – Identifying shared ancestry 37
14128 IMPUTE 4: statistical analysis of genome-wide data 38

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

INVESTORS IN PEOPLE | Silver

14526 Gap-Seq: single molecule sequencing for single-molecule phenotyping 39
14872 Sparse decomposition of arrays (SDA) 40
15513/15608/16172 Using the CHLORAD pathway to improve crop yield traits 41
15670 RELATE: estimating genome wide genealogies for thousands of whole-genome sequences 42
16224 A method for genetic modification of biofilms 43
16992 IMPUTE 5 44

IMAGING 45

2924/6596 Targeted MRI contrast agents for detection of brain tumours and inflammation 46
9030 Improved inflammation imaging 47
9564 FSL brain-mapping software 48
11771 Improved quantification of arterial blood-flow 49
11341 Smart Align: image registration software for (S)TEM images 50
12191 Off-resonance correction method for MR perfusion imaging and angiography 51
12409 Post-processing deblurring for medical imaging 52
13299 High throughput image analysis platform for 3D cellular tissues 53
13952 Targeted imaging agent as a companion diagnostic and prognostic for osteoarthritis 54
14289 Correcting imaging artefacts due to bidirectional scanning 55
15151 Non-invasive PET imaging of PARP expression 56
15727 Graphene based sensor system compatible with MRI and CT imaging 57
16185 A new method for automated 3D blood vessel reconstruction 58

METABOLIC DISEASES 59

8949 UKPDS Cardiovascular Risk engine – Version 3 60
9797 Glycaemic variability calculator 61
9965 Version 2 of the UKPDS OM – A type 2 diabetes outcomes model 62
10804 Early gestational diabetes diagnostic 63

NEUROSCIENCE 64

8818 Are you awake? Method for measuring consciousness and depth of anaesthesia 65
11128 Diagnosing neurological autoimmune disease 66
12768 Using inorganic nitrites as a marker for brain injuries caused by a stroke 67
15499 Artefact-free recording for neuromodulation devices 68
15744 Targeted drug delivery to the brain for treating neurodegenerative diseases 69
16759 An all-optical associative element 70
16952 Amyotrophic lateral sclerosis diagnostic 71
16965 Serum neuronal exosomes to improve early Parkinson's disease diagnostic 72
17514 A potential new therapeutic target for Parkinson's Disease 73
15728 A combined diagnostic approach to identify patients with CASPR2 autoantibodies 74

ONCOLOGY 75

4130/11532 Acute myeloid leukaemia prognostic and diagnostic screening 76
6855 Brain tumour detection and treatment 77
7261 Rapid, cost-effective test for T cell lymphoma and leukaemia 78
9086 Novel cancer treatment to improve the efficiency of radiotherapeutic methods 79
15395 Method to detect the Water Equivalent Path Length (WEPL) in proton CT therapy 80
15456 IGF2-TRAP: high affinity receptors to sequester growth factors linked to cancer 81

16598 A biomarker to classify colorectal cancer patients 82
17319 Remote activation and delivery of tissue-specific chemotherapy drugs 83

ORTHOPAEDICS 84

8573 Degradable implant to enhance surgical repair of musculoskeletal tissue 85
11194 OSSKAR – A positioning device for hands-free stress imaging of the knee 86
11652 Precision joint alignment for total knee replacement 87
11979 Medical device facilitating improved patient experience following joint replacement 88
12527 Improved tools for corrective surgery of the tibia 89
14859 Head extractor tool for total orthopaedic hip replacement 90
15647 Non-surgical distraction orthosis to treat hand arthritis and fractures 91

PRODUCTION/MANUFACTURING 92

14808/14955 Increasing the stability and biocompatibility of chemically synthesized oligos 93
15101 Electrocatalytic nanoparticles (Nafion ®) nanostructures doped with redox active species 94
15349 New method for the characterisation of amorphous complex mixtures 95
16771 Bespoke reference electrode for electrochemical sensors 96
17477 Stabilised viral fusion proteins 97

RESEARCH TOOLS 98

10098 Nanoparticle detection 99
10126 IMPACT: Rapid calculation of protein structural parameters 100
12370 Protein team assembly for controlling cell signalling and catalysis 101
12970 MAGMA: Automated assignment of NMR spectra for proteins and complexes 102
13366 EMΠIM: Correlating electron microscopy (EM) and ion mobility (IM) spectra 103
13367 BiobOx: A flexible tool for structural biology 104
13871 Multipurpose magnetic microparticles 105
14348 SpyTag and SpyCatcher version 2.0 106
14383 SnoopLigase for catalysis of ligation between two peptide tags 107
15033 Electrochemical oxidase test for identifying and quantifying bacteria 108
15681 Rapid detection of developed viruses and lipid-coated nanoparticles 109
16405 INDIANA - IN-cell DIffusion ANAlysis 110
16826 A new form of natural elastin with gel-like properties 111
16887 Multi-functional air flow thawing apparatus 112
17035 A Polymer coating that is selectively sticky for water but not oil 113
17072 Rapid high precision microencapsulation for controlled release 114

SOFTWARE 115

12350 HTSense: Simplifying the analysis and design of high throughput screens 116
14419 Quantiphyse - Improved analysis of biomedical imaging data Technology 117
14458 Motion sickness solution for electronic device use 118
14605 Improved cross-linking models between amino acids with DynamXL software 119
14905 AFIRM: Amyloid Formation and Inhibition Mechanism 120
16245 Virtual Assay drug screening software V3.0 121
16385 An early warning system to predict clinical deterioration 122
17185 Curator: Software for the advanced curation of real-world clinical data 123

16385 Career Weaver: A web based application to identify core career drivers 124
20120 Computational antibody modelling and prediction – SAbPred singularity platform 125

TARGETED THERAPIES 126

7876 An extracellular blocker of the K30 polysaccharide transporter Wza 127
13911 Gene therapy for chronic pain and epilepsy 128
15877 Extracellular vesicle loading technology 129
16008 Base editing proteins to repair mutations in the haemoglobin gene 130

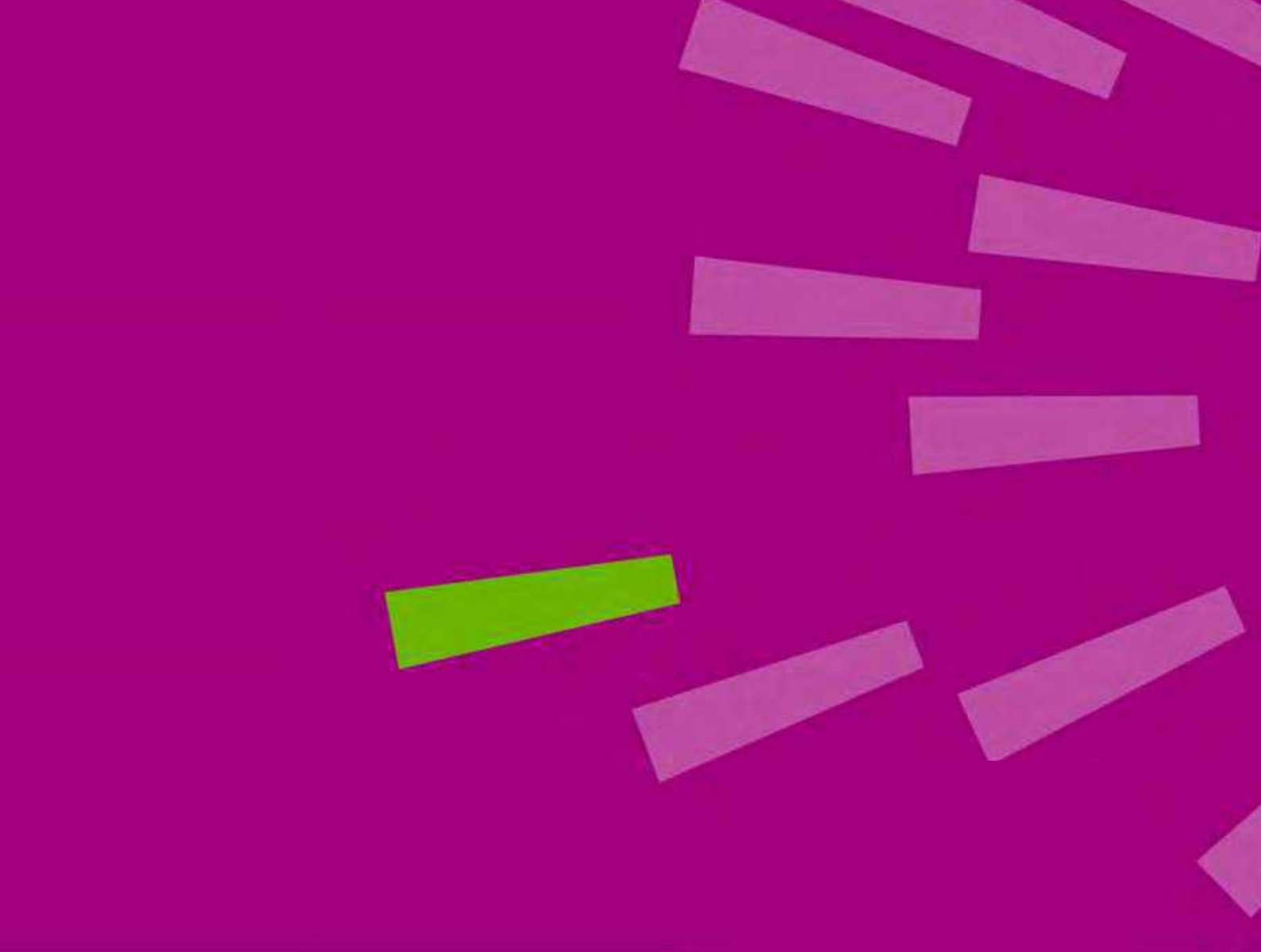
VACCINES 131

7968 S-FLU: Broad spectrum flu protection with a superior safety and delivery profile 132
10355 Hepatitis C vaccine 133
10599 HIV vaccine 134
11715 Multivalent Dengue vaccine 135
13214 A novel immunisation methodology 136
13769 Zika viral vector vaccine 137
14762 Plasmid stabilisation for use in Shigella vaccine development 138

COA – CLINICAL OUTCOMES ASSESSMENT 139

ALSAQ The Amyotrophic Lateral Sclerosis Assessment Questionnaire 140
CDAQ The Coeliac Disease Assessment Questionnaire 141
DHP-18 The Diabetes Health Profile 142
DMD-QoL Duchenne Muscular Dystrophy Quality of Life Measure 143
DSMT-Q Diabetes Self Management Technology Questionnaire 144
EHP The Endometriosis Health Profile 145
HASMID-10 Health and Self-Management in Diabetes 146
LTCQ Long-Term Conditions Questionnaire 147
LUNSERS The Liverpool University Neurologic Side Effects Rating Scale 148
MAAQ Mathematics Attitudes and Anxiety Questionnaire 149
MCQ The Mild Cognitive Impairment Questionnaire 150
MFPDI The Manchester Foot Pain and Disability Index 151
MIDAS The Myocardial Infarction Dimensional Assessment Scale 152
MOxFQ The Manchester-Oxford Foot Questionnaire 153
MSK-HQ Musculoskeletal Health Questionnaire 154
OACS Oxford Arthroplasty Early Change Score 155
OARS The Oxford Arthroplasty Early Recovery Score 156
OCS The Oxford Cognitive Screen 157
ODQ The Oxford Depression Questionnaire 158
OES The Oxford Elbow Score 159
OHS The Oxford Hip Score 160
OKS The Oxford Knee Score 161
OKS-APQ Oxford Knee Score –Activity and Participation Questionnaire 162
OSIS The Oxford Shoulder Instability Score 163
OSS The Oxford Shoulder Score 164
OxAFQ-C The Oxford Ankle Foot Questionnaire for Children 165
Ox-PAQ The Oxford Participation and Activities Questionnaire 166
PDQ The Parkinson's Disease Questionnaire 167

PDQ-C Parkinson's Disease Questionnaire – Carers 168
PDQ-Exercise Parkinson's Disease Questionnaire - Exercise 169
PostopQRS Postoperative Quality of Recovery Scale 170
PREOS-PC Patient Reported Experiences and Outcomes of Safety in Primary Care 171
ReQoL Recovering Quality of Life Questionnaire 172
WHQ The Bluebelle Wound Healing Questionnaire 173



INFLAMMATORY DISEASES

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

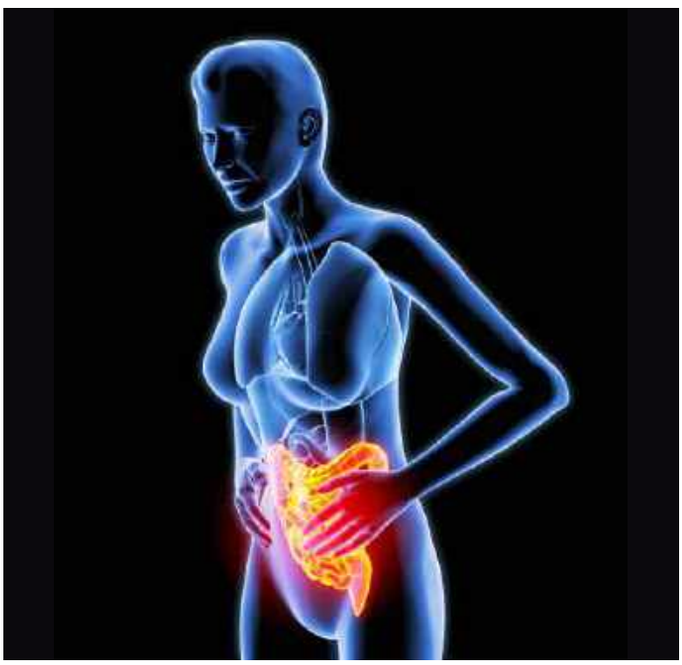
Researchers at Oxford University have identified a potential new target for IBD therapeutics; they found Oncostatin-M (OSM) to be a major component of the cytokine response in the Th17 inflammatory pathway. This pathway is thought to be critical in the pathogenesis of IBD, therefore targeting OSM or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

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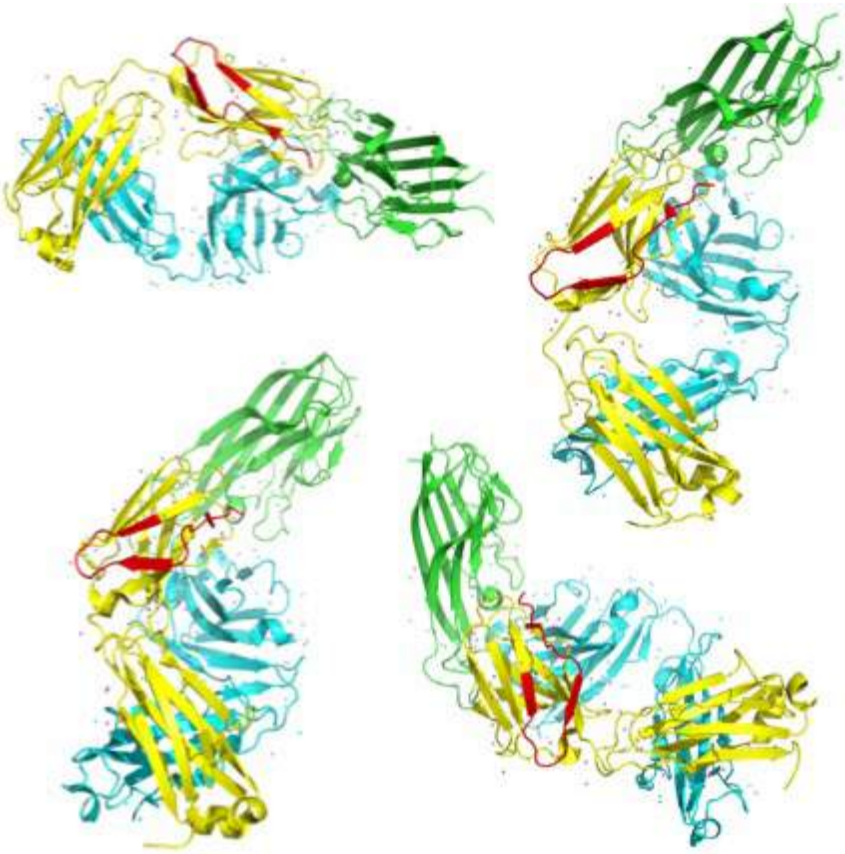
Improved anti-TNF Antibodies

Researchers at Oxford have identified the potential immunogenic regions on the anti-TNF antibody, Infliximab, which could be modified to decrease immunogenicity-based drug failure.



Immunogenetic drug failure

Inflammatory Bowel Diseases affect the GI tract and include diseases such as Crohn's and ulcerative colitis. Global prevalence is on the rise and currently highest in Europe and North America, now affecting approximately 0.5 to 1.0% of the adult population in the UK. Although there is no cure for IBD, several therapies have been developed to induce and maintain remission.

Some of these treatments, such as infliximab, are monoclonal antibodies against Tumour Necrosis Factor. Although highly effective in some individuals, the success of these drugs is limited by primary non-response as well as secondary immune-mediated loss of response, affecting 24-46% of patients in the first year of use.

This non-response renders these treatments ineffective, making treatment for these individuals, who are thought to be genetically susceptible to non-response, more complex.

New and improved

Oxford researchers have identified possible key regions for modification in both the adalimumab (Humira) and infliximab (Remicade) monoclonal antibody, often used to treat a variety of autoimmune diseases such as IBD.

The modifications edit unique amino acid sequences on the infliximab light and heavy chain, tackling any immunogenicity related non-response. These regions include the N-terminal region of the light chain and just downstream of the N-terminal region of the heavy chain.

Therapeutic use

Commercial use of an antibody modified based on the researchers' specifications would focus mainly on treatment for Crohn's disease and ulcerative colitis patients. However, this invention may likely be beneficial in the treatment of a broad spectrum of autoimmune diseases.

For further information please contact:

enquiries@innovation.ox.ac.uk
+44 (0)1865 280830
www.innovation.ox.ac.uk
Project number: 17118

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DATA MANAGEMENT TOOLS

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:

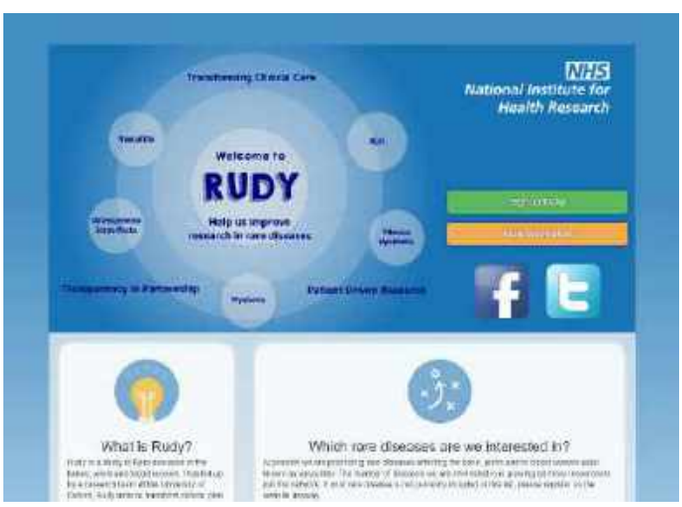
- Enables secure encryption of all patient identifiable information
- Designed with the users in mind
- Built in a framework that allows easy addition of functionality
- Operates through dynamic consent
- Allows patients to access their own data anywhere, anytime
- High patient recruitment and retention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

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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.

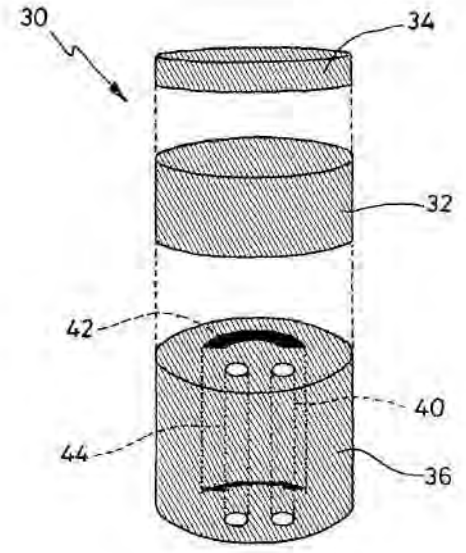

Figure 1

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

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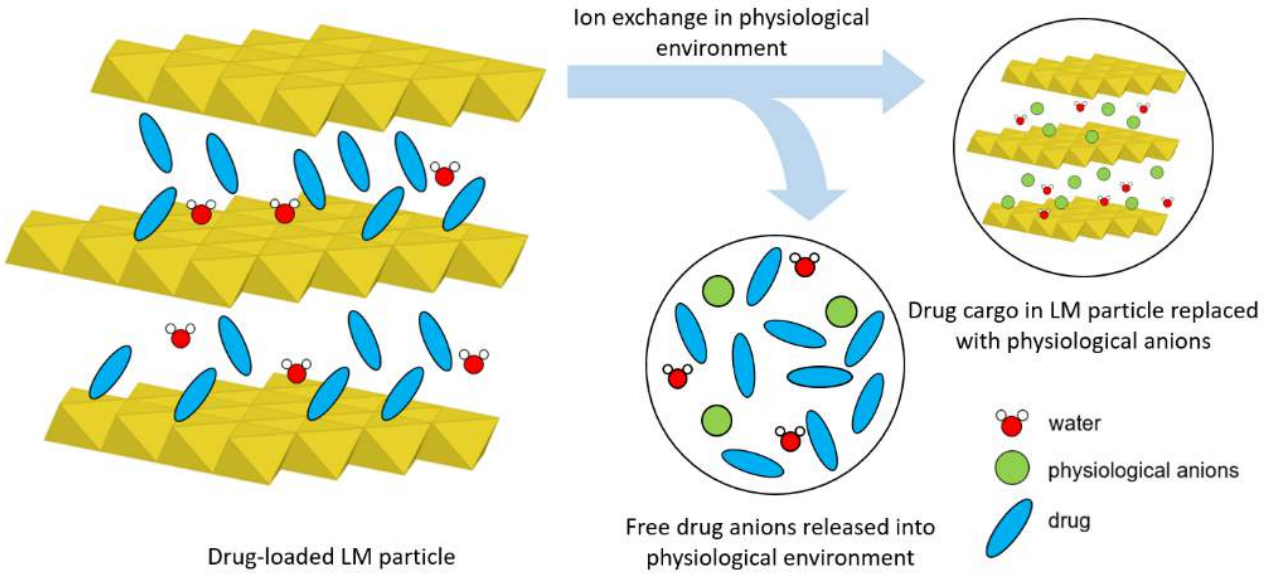
Layered double hydroxides

Researchers at the University of Oxford have a new method which uses layered double hydroxides (LDHs) as an oral drug delivery system.



Layered double hydroxides (LDHs) are a class of compounds that comprise two metal cations and have a layered structure. These materials are of significant technological importance in diverse areas such as catalysis, optics, medical science, and separation science. The application of LDHs in separation science has recently highlighted their role as fast, efficient, high-capacity ion-exchange materials.

Researchers at the University of Oxford have developed a novel method using LDH compounds in the manufacturing of drug delivery systems. The present invention is based on the discovery that a pharmaceutically active compound having at least one anionic group can be intercalated into an LDH compound and that the intercalate releases the pharmaceutically active compound in a controlled manner when subjected to low pH conditions that may prevail inside the stomach of a patient.

It is known that certain pharmaceutically active compounds, when administered orally, may cause both an unpalatable taste sensation and irritation of the stomach. Some patients are, of course, more vulnerable to irritations of this kind than others and unacceptable taste/ palatability is a particularly important issue for the administration of oral paediatric medicines. By controlling the release of such compounds in the stomach these effects can be avoided or at least reduced.

Advantages as a Release System:

- Confinement of the “active agent” between the metal hydroxide layers restricts molecular interactions and dynamics and may improve the long-term stability compared to the existing formulations.
- The antacid performance and pH stability are also controllable by the choice of metal ions in the host layers.
- Control of the point of release and pharmacokinetic profile by control of the metal ions in the host layers.
- New formulation may extend patent protection over existing generic formulations.
- High loading of “active agent”, up to 50% can be achieved.
- Taste masking.

LDHs are not limited to drug delivery systems and have many other potential applications. Oxford University Innovation has patented the storage and controlled release of ions from LDHs.

For further information please contact:

enquiries@innovation.ox.ac.uk
+44 (0)1865 280830
www.innovation.ox.ac.uk
Project number: 0957

Technology Transfer from the University of Oxford

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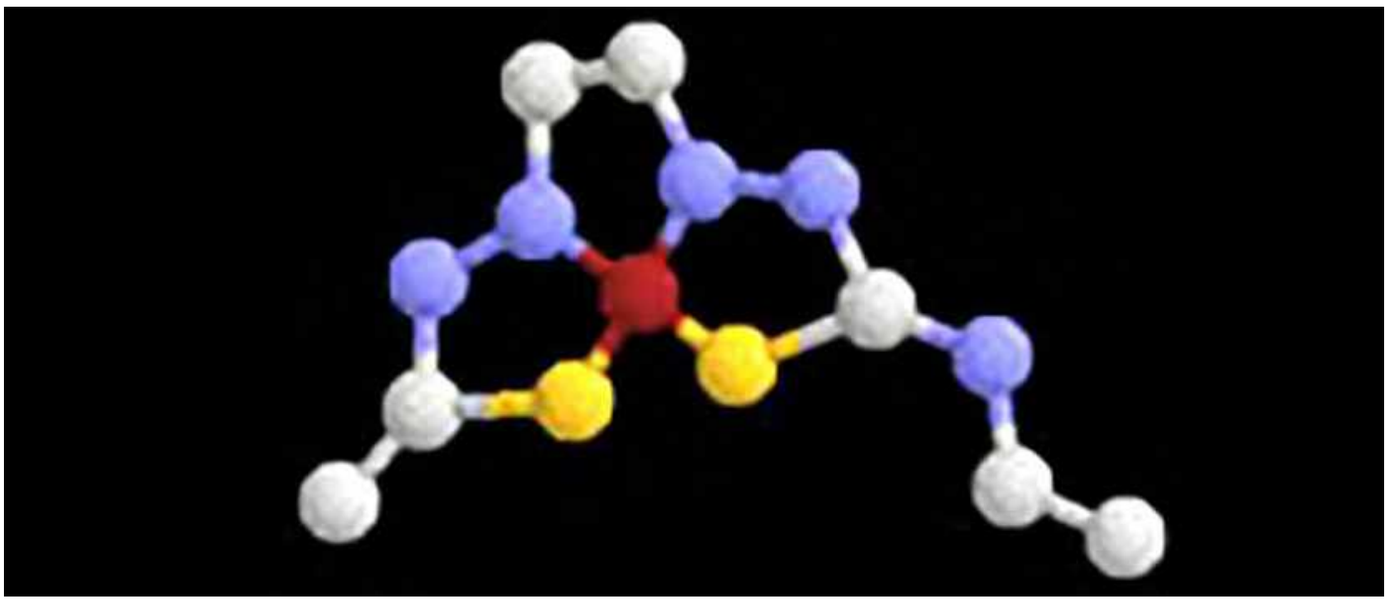
Saliva drug testing

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

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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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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

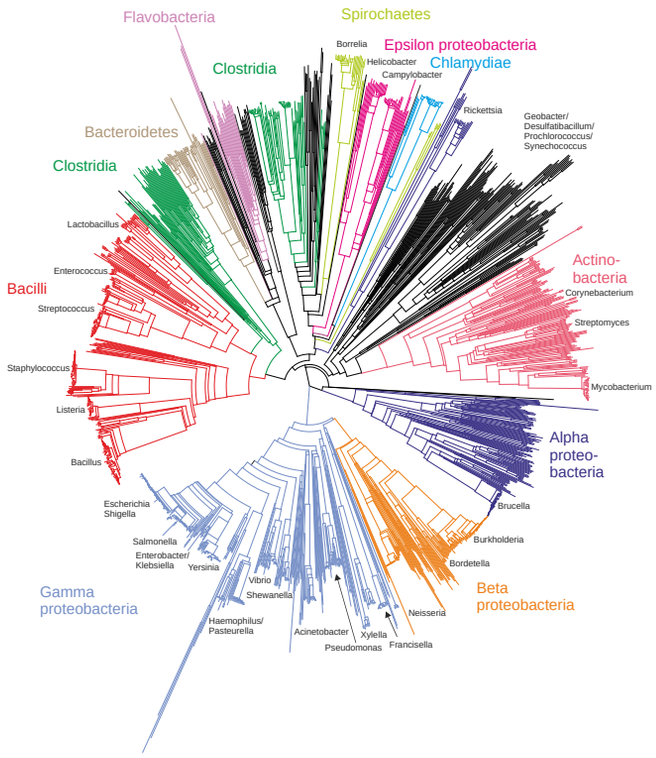
A web-accessible and expandable database comprising genome data from more than 2000 bacterial isolates has been generated. The variation of 53 rps genes is catalogued in this database, providing a means of defining the precise phylogenetic position of any bacterial sequence at the domain, phylum, class,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

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Metal-free Catalysts

Oxford scientists have developed a novel class of metal-free catalysts based on Frustrated Lewis Pair chemistry, which offer excellent activity and selectivity in industrially applicable hydroboration and dehydrogenation reactions.

Transition-metal catalysis

Transition-metal catalysts are extensively used in large-scale industrial processes in the pharmaceutical industry. The use of homogeneous catalysts for such transformations offers a number of advantages, including excellent activity and selectivity under mild conditions, and in the presence of sensitive or reactive functional groups.

The ability to readily tune the reactivity of the metal-centre through selection of the appropriate ligands is also a major factor in the diverse range of applications that have been found for such catalysts.

Transformations facilitated by transition-metal catalysts underpin the majority of synthetic routes to pharmaceutically active compounds.

Towards a sustainable future

Despite the evident advantages of using transitionmetal catalysts in synthesis, there are issues with cost, toxicity, and sustainability. Some of the most widelyused homogeneous catalysts are based on metals that will potentially become unavailable in the next 30 years, as commercially viable deposits become exhausted.

Many transition-metals are toxic, and regulatory controls require their removal from pharmaceutical products. This adds a step to the production process, and therefore additional cost. Sustainable, non-toxic alternatives are, therefore, of significant interest to the industry.

A new class of metal-free catalysts

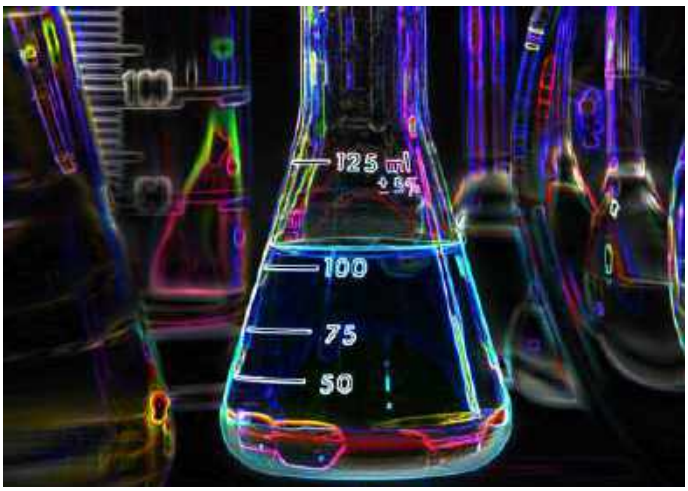
Oxford researchers have developed a new class of metal-free catalysts, offering excellent activity in selective hydroboration and dehydrogenation reactions. The reactivity of the catalysts is based on “Frustrated Lewis Pair” chemistry, and offers the following features:

- Metal-free system
- Highly tuneable reactivity
- Selective hydroboration under mild conditions
- Tolerant to sensitive functional groups
- Low catalyst-loadings
- Modular design to fit a range of applications

The Oxford compounds also demonstrate activity in C-H bond activation under mild conditions and the potential to activate a range of small molecules, such as CO_2 and CO. The dehydrocoupling reactions can also be used to produce polymers with inorganic backbones, offering applications in electronic devices.

Commercialisation

The compounds and applications thereof, are the subject of a UK priority patent application with the potential for international coverage. The activity of the catalysts towards hydroboration and dehydrogenation has been extensively tested and work is ongoing to uncover the full potential of this new class of molecules. Oxford University Innovation is seeking industrial partners to support commercialisation of this technology.



For further information please contact:
Marina Fuentes Sainz
marina.fuentessainz@innovation.ox.ac.uk
+44 (0)1865 614423
www.innovation.ox.ac.uk
Project number: 12408

Technology Transfer from the University of Oxford

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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

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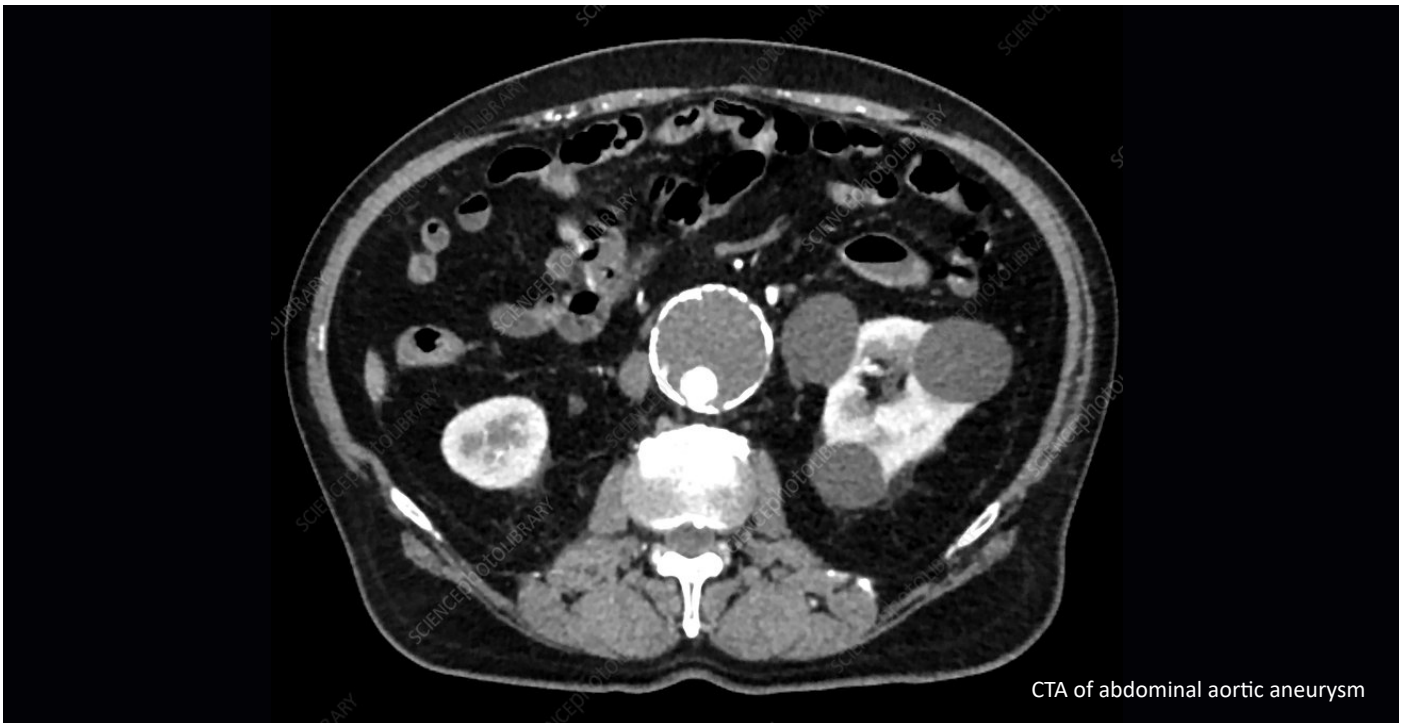
Growth prediction of abdominal aortic aneurysms

Researchers at the University of Oxford have developed a method for determining the predictive rate of growth of abdominal aortic aneurysms (AAA).



CTA of abdominal aortic aneurysm

What is an 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 programmes 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.

AAAs 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.

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 AAAs. The method developed by the Oxford team is the first step towards personalised management for patients with AAAs.

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: 13022

Technology Transfer from the University of Oxford

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A Microfluidic Sonication Device for the Production of Coated Microbubbles

Available to license: A novel way of producing microbubbles which have many applications, particularly in the field of medicine.

The Oxford Team has developed a platform technology that could be used in a clinical setting to produce microbubbles employed as contrast agents in ultrasound imaging or as drug delivery vehicles.

Gas-filled microbubbles

Gas-filled microbubbles stabilised by a surfactant or polymer coating are routinely used in medical imaging as ultrasound contrast agents, being capable of enhancing ultrasound backscatter from blood by several orders of magnitude. Furthermore, the microbubble shell can be employed as a scaffold for transporting biologically active compounds or targeting agents in the circulation, which has opened the way for the use of microbubbles as vehicles in therapeutic applications such as drug delivery or gene therapy. However, the acoustic response and therefore the clinical utility of microbubbles are profoundly influenced by their physical characteristics, including size, size distribution, and the mechanical properties of the coating layer. Therefore, there is a need for a system which offers tighter control over microbubble properties to maximise their clinical effectiveness.

Manufacture of microbubbles

For the majority of applications, microbubbles are currently fabricated using standard emulsification methods such as sonication which results in highly heterogeneous microbubble populations in terms of size, surface properties, and stability/dynamic response and loading of e.g. drugs for therapeutic applications. Over the past 10 years microfluidic devices have been explored as an alternative but whilst these offer excellent control over microbubble size, they suffer from low production rates, short device life time, and poor control over microbubble surface properties.

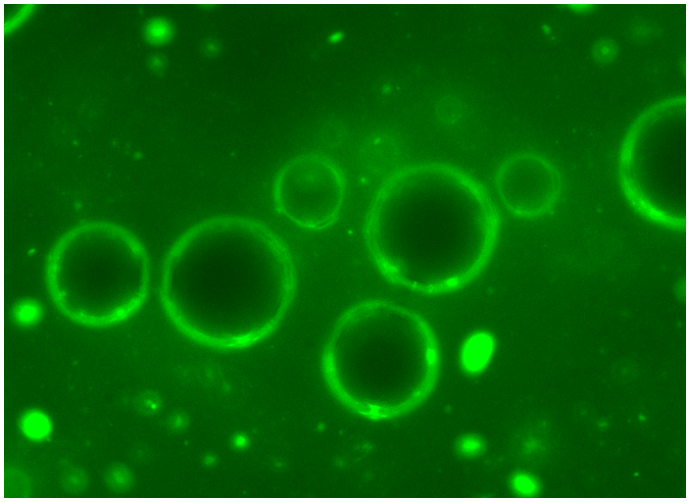
Advantages of the Oxford system

Compared to conventional methods, the Oxford approach offers the advantage of higher control over the properties of the physical environment in which microbubble formation occurs, allowing for improved reproducibility between experiments and narrower microbubble size distribution.

As well as being easy to operate, the system also offers superior device lifetime and low fabrication costs.

Furthermore, the parameters in the system can be finely adjusted in order to optimise the characteristics of the finished product, such as microbubble size, size distribution and concentration, and physical properties of the microbubble shell which are key determinants of microbubble stability and response to ultrasound.

Oxford University Innovation is looking to speak with parties interested in developing or licensing this technology. The technology is subject to a patent application.



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: 13067

Technology Transfer from the University of Oxford

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Smart mouth guard

Researchers based at Oxford University have developed a smart mouth guard, which allows the wearers to monitor and track their performance and physical exertion on the field.

Participation nation

In 2016, around 16 million adults in England were engaged in sporting activities on a weekly basis, with contact sports such as Rugby, seeing an increase of up to 25% compared to the previous year (Active People Survey). Having the correct protective equipment is crucial to ensure the safety of these inherently dangerous pursuits. For example, mouth guards are used to protect wearers' teeth and help prevent concussions, with approximately 40 million mouth guards being sold in the US every year.

Performance monitoring

At both an elite and amateur level there is a desire for sports people to gather data on their health and performance. In 2016 alone, around 80 million sports wearable units were sold worldwide. Smart watches and heart monitors have led the way in this regard, however there has been little work on providing intelligent protective equipment.

Smart mouth guard

Oxford researchers have developed a smart mouth guard that not only offers protection but also allows the wearers to monitor and track their sports performance without wearing an extra, bulky device. The mouth guard measures several physical parameters and transfers the information wirelessly to a mobile device. We believe the main benefits of the device to be as follows:

- Discrete and easily used
- Measures several parameters simultaneously
- Data analysis software provided
- Detects perceived and actual fatigue
- Prevents injuries through digital and physical means

Commercialisation

This technology is subject to a patent application. Oxford University Innovation would like to speak to companies who are interested in commercialising 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: 13151

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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

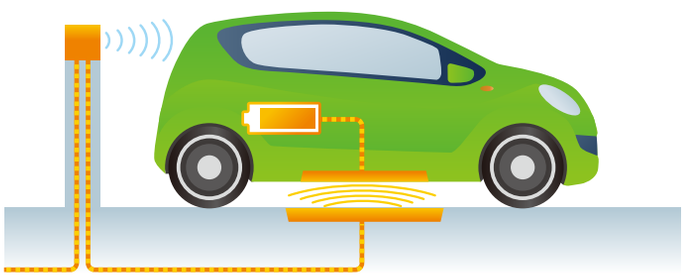
Researchers at the University of Oxford have developed a sensor, based on nuclear quadrupole resonance (NQR), capable of detecting biological material in proximity to the WPT field. The NQR system differentiates between humans or animals and can provide feedback to the WPT device to trigger a shut-down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

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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

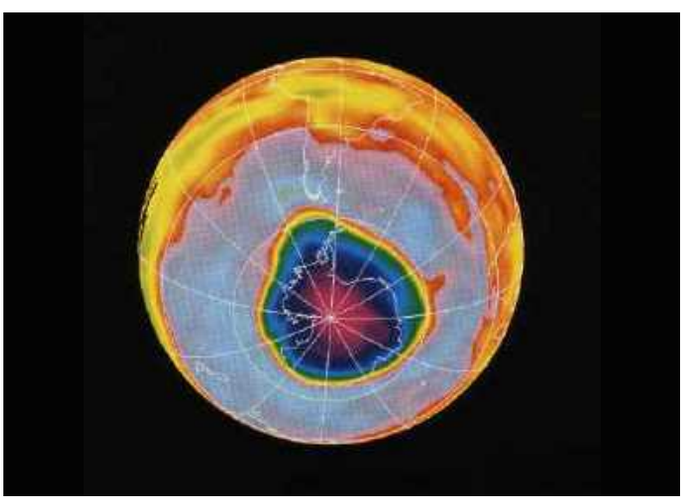
The device can detect molecules that are a few atoms in size, up to those as large as proteins but could also be used to detect electromagnetic radiation. The technology can be adapted to detect specific chemical functional groups. This adaptability enables the device to perform in many different applications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

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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.

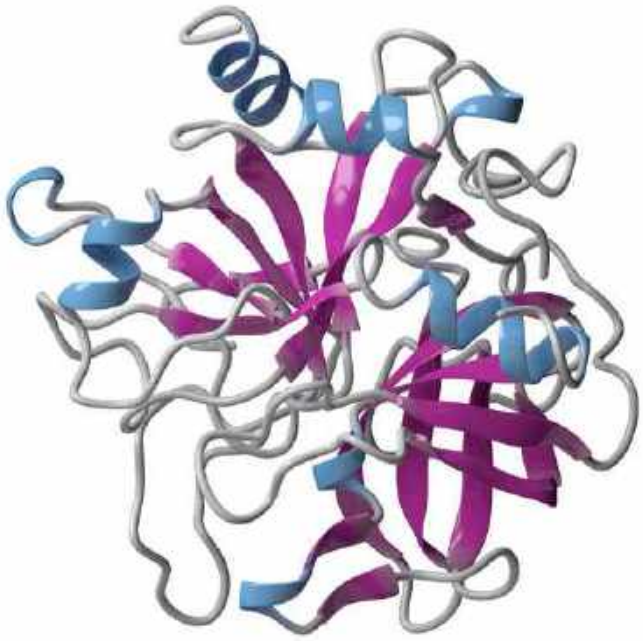
Surgical repair of the pseuodaneursysm requires general anaesthetic and can be complicated by infection of the wound and prolonged hospital stay for aftercare. Ultrasound guided mechanical compression is often avoided as the area affected is often swollen and tender.

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

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Automated detection of bacterial growth from a photograph of a 96 well plate

Researchers at the University of Oxford have developed software to read digital images of microbial growth under different antibiotic conditions.

Controlling antibiotic usage

Antibiotic resistance is one of the most pressing public health problems around the world. Resistance arises when bacteria change and continue to multiply in the presence of therapeutics levels of an antibiotic. Although resistance is a natural process, it develops more rapidly through the misuse and overuse of antibiotics. Therefore great care needs to be taken in selecting the correct antibiotics for treating each infection.

High throughput screening

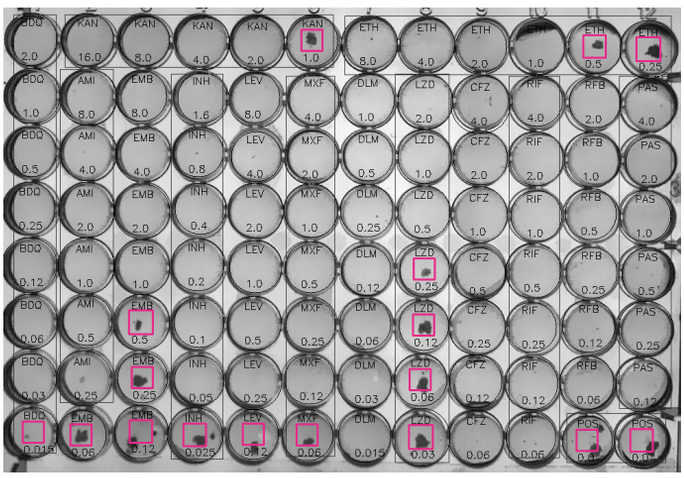
Microtitre plates are standard equipment in both clinical and research laboratories. They allow microbiologists to carry out large numbers of drug susceptibility testing on small amounts of material in a high throughput manner, thus giving clinicians rapid feedback on the most appropriate treatment for a given infection. Many laboratories use automated systems for filling and incubating the plates that can contain thousands of wells. However, analysis of the results of such studies is generally done by eye and is prone to mistakes. A more reliable way to measure the amount of bacterial growth would be of great benefit.

Image processing of 96-well microtitre plate

Researchers at the University of Oxford have developed a software solution capable of interpreting the results of antibacterial assays carried out in 96-well plates. The technology makes use of existing camera infrastructure, but can significantly decrease the amount of human time required. Whilst this technology has been developed primarily for antibiotic susceptibility testing using *M. tuberculosis*, it could also be used for *Bacillus subtilis*, *Staphylococcus aureus* and other circular forming bacterial colonies. This technology has been validated so far on more than 24,000 independent measurements of minimum inhibitory concentration (MIC).

The main benefits of the technology are:

- Rapid and accurate analysis of a photograph of 96-well plate assays
- Reduction of subjective nature of tests
- Low cost implementation
- Makes use of existing plate reader and image capture infrastructure
- Applicable to a research or clinical setting



For further information please contact:
Bénédicte Menn
benedicte.menn@innovation.ox.ac.uk
+44 (0)1865 280906
www.innovation.ox.ac.uk
Project number: 14654

Technology Transfer from the University of Oxford

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Deep clustering for phenotyping complex diseases

Oxford researchers have developed an automated modelling platform for detecting the phenotypic subgroups in patients suffering from complex diseases.

Classification of phenotypic types and subtypes is important for both clinical care and research into underlying disease mechanisms. Detecting phenotypic subgroups of patients suffering from complex diseases for example Parkinson's disease and Chronic obstructive pulmonary disease could provide support for early detection of deteriorating patients, determination of individualised and customised treatment, and prevention strategies for different phenotypic groups, which ultimately results in enhanced treatment outcome.

Scientists at the University of Oxford have developed an end-to-end pipeline composed of data collection, pre-processing and data modelling which can identify patients with complex diseases into subgroups with differing disease progression and risk of disease complications.

The sub-stratification of diseases enables screening of risk factors (genetic and/or environmental), tailor and target early treatment for patients in a way towards precision medicine with more efficient healthcare delivery and further improved patient outcome.

The technology allows for an integrated platform for precision medicine, more specifically using the architecture of deep clustering to subtype a disease patient cohort with phenotypic information that has genetic associations with clusters.

The technology has application in a variety of precision medicine settings including drug discovery and wearable health monitoring.

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: 15739

Technology Transfer from the University of Oxford

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Probabilistic clustering of signatures

Oxford researchers have developed machine learning tools to identify the phenotypic subgroups in patients with complex diseases using circadian hospital-summary patient data.

Scientists at the University of Oxford have developed machine learning tools to identify the phenotypic subgroups in patients with complex diseases using circadian hospital-summary patient data. This technology enables to infer clusters of signatures in relation to disease and co-morbidities.

Classification based on phenotypic subgroups in patients could be used to aid effective selection of treatment plans or more efficiently detect heightened risk of adverse medical events or abnormalities. Various approaches are known for classifying the health of a patient using measurements of vital signs, but most of them are either heuristic or assume that data is time invariant and independent. Furthermore, such vital sign measurements commonly contain different numbers of observations, and at irregularly sampled times.

Oxford researchers have developed a range of machine learning technologies that overcome these problems. They have developed an end-to-end pipeline composed of data collection and processing techniques to generate the signatures and personalised data modelling which can serve towards preventative and prevision medicine. Such a pipeline could significantly improve patient outcomes and boost hospital performance.

The invention is an integrated platform for pattern recognition of patient signatures, patient phenotype discovery and patient risk stratification. There is currently no means for analysing circadian signatures of patient data in such a robust manner. This clustering method is particularly well-suited to real-world clinical data, whereby it can handle the missing aspects that typify such real-world data, and which is a key component of the tools.

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: 15740

Technology Transfer from the University of Oxford

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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:
Amelia Griffiths
amelia.griffiths@innovation.ox.ac.uk
+44 (0)1865 280842
www.innovation.ox.ac.uk
Project number: 15823

Technology Transfer from the University of Oxford

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Patient flow management system for hospitals and emergency departments

Oxford researchers have developed an integrated management tool for optimising patient flow across a hospital setting.

A busy hospital environment often requires GPs and nurses to diagnose, treat, and provide a comfortable place for patients to recover. A hospital wide system with complete knowledge of all its patients could provide an optimal 'global' solution to busy clinicians.

Patient flow, the ease with which a patient moves throughout the different stages of a medical facility without being subject to or causing delays, has many contributing factors. Current approaches to managing patient flow are often reactive, which can result in suboptimal performance and significant delays in the patient's care and eventual discharge. This is a particular problem in A&E departments where timescales are shorter and decisions need to be made quickly. This is becoming increasingly important as population growth and ageing impact heavily on patient flow within a hospital.

The technology which has been developed will be instrumental in enabling proactive hospital management of patient care pathways, thereby improving patient flow through the reduction of unnecessary delays and wait times. Predicting admission numbers and likely care pathways for admitted patients allows necessary steps required for the care of these patients to be taken proactively and ahead of time, rather than reactively.

Furthermore, identifying and ranking patients ready to be discharged will provide further utility as it will allow doctors to prioritise the discharge of patients considered most likely ready for discharge, thereby freeing up hospital beds for incoming patients.

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: 15840

Technology Transfer from the University of Oxford

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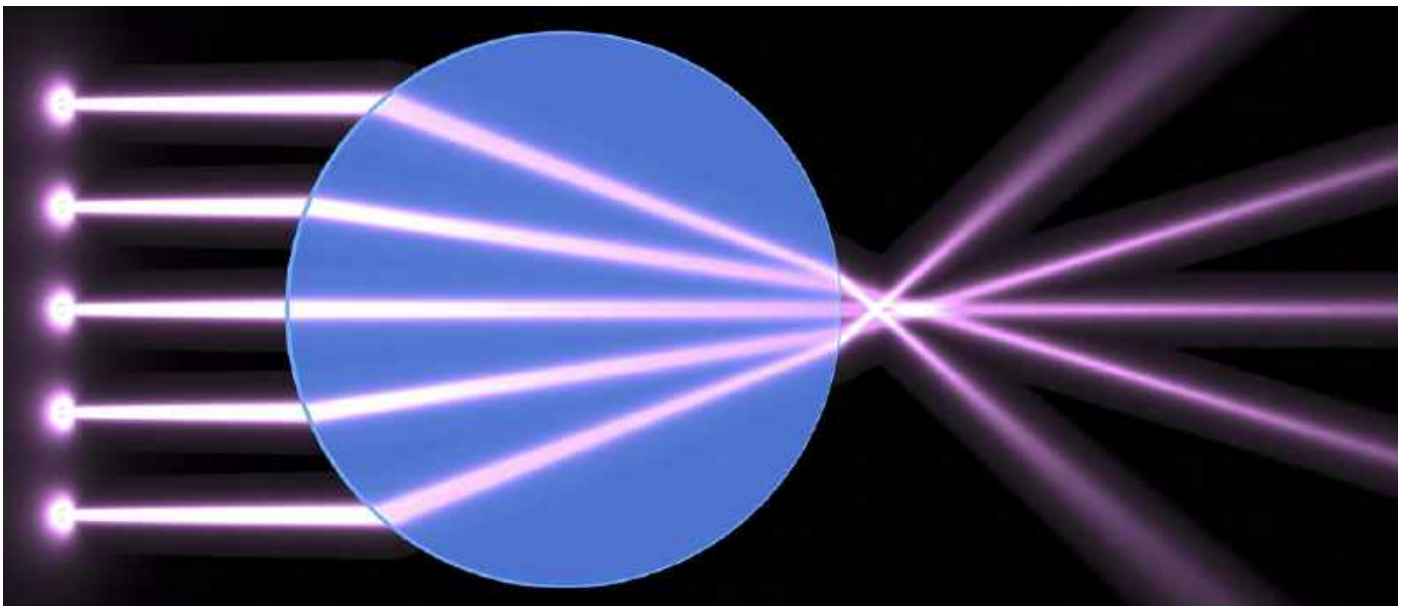
Multifunctional device for focusing light through an optical component

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:
Rachel Grovenor
rachel.grovenor@innovation.ox.ac.uk
+44 (0) 7551 372293
www.innovation.ox.ac.uk
Project number: 16143, 16372

Technology Transfer from the University of Oxford

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A new dual-channel needle for the extraction of oocytes during the IVF process

Oxford researchers have developed a new type of dual-channel needle for the extraction of oocytes during IVF with a significantly improved oocyte yield.

Background

The World Health Organisation estimates that 10% of women suffer with subfertility worldwide. In vitro fertilisation (IVF) has revolutionised the field of reproductive medicine, giving couples struggling to conceive the chance to have a baby.

On a European level, data from 2014 indicated that more than 500,000 treatment cycles were performed. In the USA, the equivalent number from 2016 is in excess of 250,000 cycles.

The latest data from the UK, dating from 2016, show that just over 68,000 treatment cycles were conducted leading to 20,028 live births.

The Problem

Even though the number of cycles continues to increase on a worldwide basis, it is evident that there remains significant room for improvement of the live birth rate as a proportion of IVF cycles.

The relationship between oocyte yield and live birth rate has been established in several high-quality reviews. Although biologically plausible, a Cochrane systematic review has demonstrated that follicular flushing does not have an impact on either oocyte yield or live birth rate.

Using parametres reflective of real-life conditions through high-fidelity computer simulation, researchers at the University of Oxford have modelled a typical existing dual-channel oocyte retrieval needle system. This demonstrated approximately a 66% oocyte yield with a proportion of oocytes being crushed against the needle apparatus.

The Solution

A new type of dual-channel oocyte retrieval needle has been developed by a multi-disciplinary team of researchers at the University of Oxford demonstrating an improvement of oocyte yield up to 100%. Furthermore, the new needle system significantly reduces the chance of damage to the oocyte and the corona radiata.

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: 16684

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Classification of electrocardiogram datasets

End-to-end deep neural framework that can be used for biosignal waveform analysis to classify heart disease using ECG.

The rising prevalence of chronic diseases

One of the challenges we face as global citizens is the delivery of healthcare to an ageing and expanding population. Chronic diseases are the leading cause of death for both developed and developing countries, representing 70% of all deaths, and cardiovascular disease (CVD) accounts for most of these (17.9 million annually). It is estimated that 85% of CVD deaths are due to heart attacks (i.e. myocardial infarctions) and strokes.

Traditional diagnosis of CVDs such as myocardial infarction mainly employs interpretation of electrocardiogram (ECG) recordings and blood tests, which requires precise acquisition devices and clinical expertise.

Diagnosis is difficult to achieve in a timely manner due to the slow generation of results from laboratory tests, as well as the inter-observer variability in ECG interpretation resulting in disagreement of diagnosis.

Putting AI at the heart of health care

There is a need for providing methods using machine learning algorithms with improved ability to classify ECG datasets, particularly for detection of heart disease.

Scientists at the University of Oxford have developed an improved and accurate method to classify ECG datasets. Applying these machine-learning algorithms to the combined datasets from multiple ECG leads means that correlations between the data from different leads can be taken advantage of to improve classification of the ECG dataset of the patient.

For further information please contact:

enquiries@innovation.ox.ac.uk
+44 (0)1865 280830
www.innovation.ox.ac.uk
Project number: 16879

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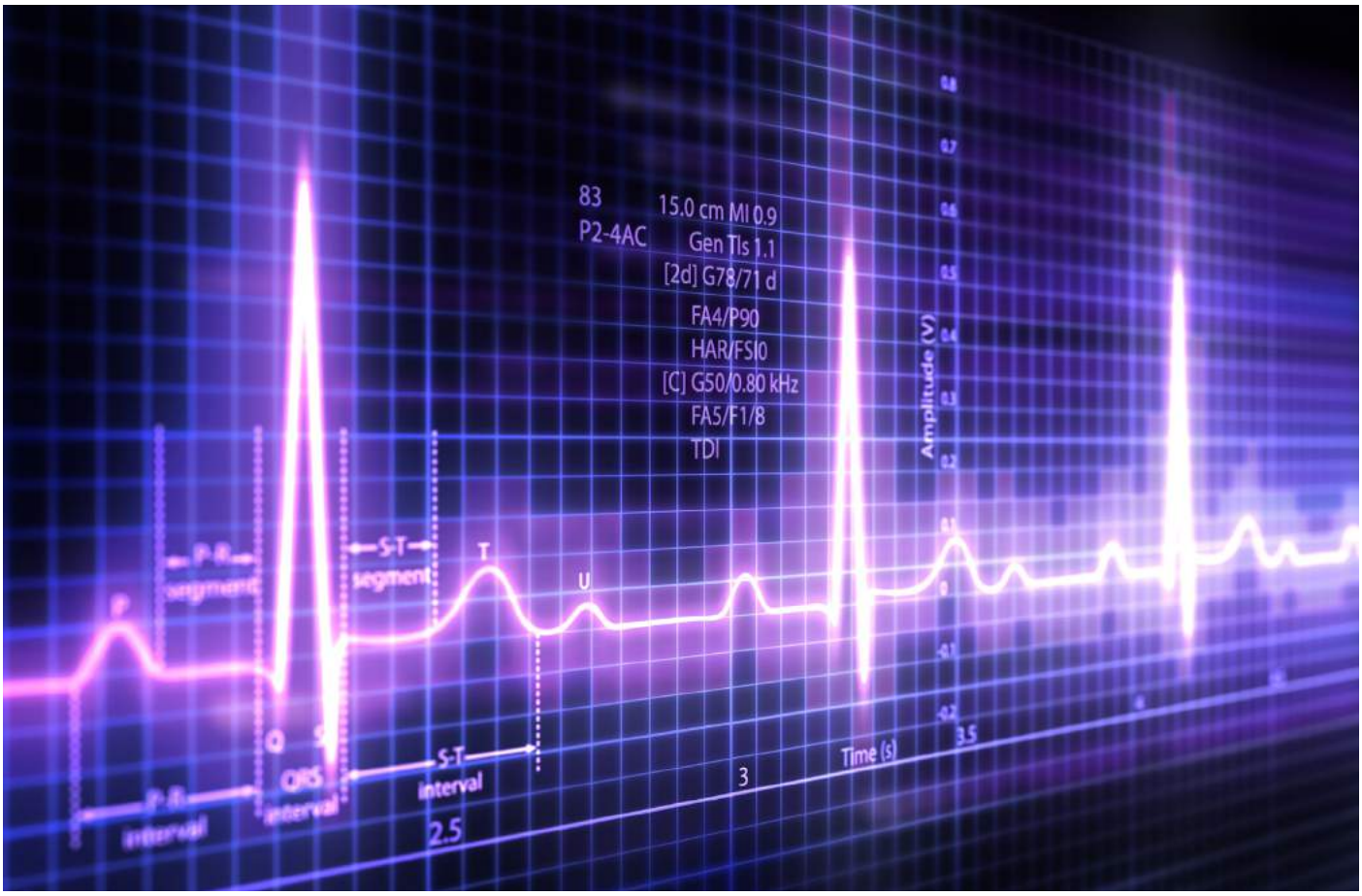
An automated deep learning system for ECG classification

Scientists at the University of Oxford have developed a method to classify electrocardiogram (ECG waveforms).



Scientists at the University of Oxford have developed a method to classify physiological data from a patient. This method relates to a range of processes received from physiological data, generated on a neural network and uses the neural network to classify electrocardiogram (ECG waveforms).

A novel network design has been developed by the Oxford team to ensure that the network has an architecture that optimises performance and accuracy over conventional models. Neural networks generated in this way provide improved performance and accuracy when applied to the classification of physiological data from a patient that overcome the problems associated with previous designs.

Current state-of-the-art neural network design approaches are trial and error which will take experienced practitioners weeks and months to develop.

The technology developed by the Oxford team can automatically generate neural networks in as little as two hours and outperforms current state-of-the-art models by a considerable margin. An advantage of the “self-configuring” architecture is the ability to construct new network designs rapidly when there is a need for new models; e.g., when new pathologies are added, or even when new diseases/ comorbidities are considered.

Furthermore, this technology has particular application in aiding medical professionals in the diagnosis of clinical data by classifying the input into clinical categories.

For further information please contact:

enquiries@innovation.ox.ac.uk
+44 (0)1865 280830
www.innovation.ox.ac.uk
Project number: 17132

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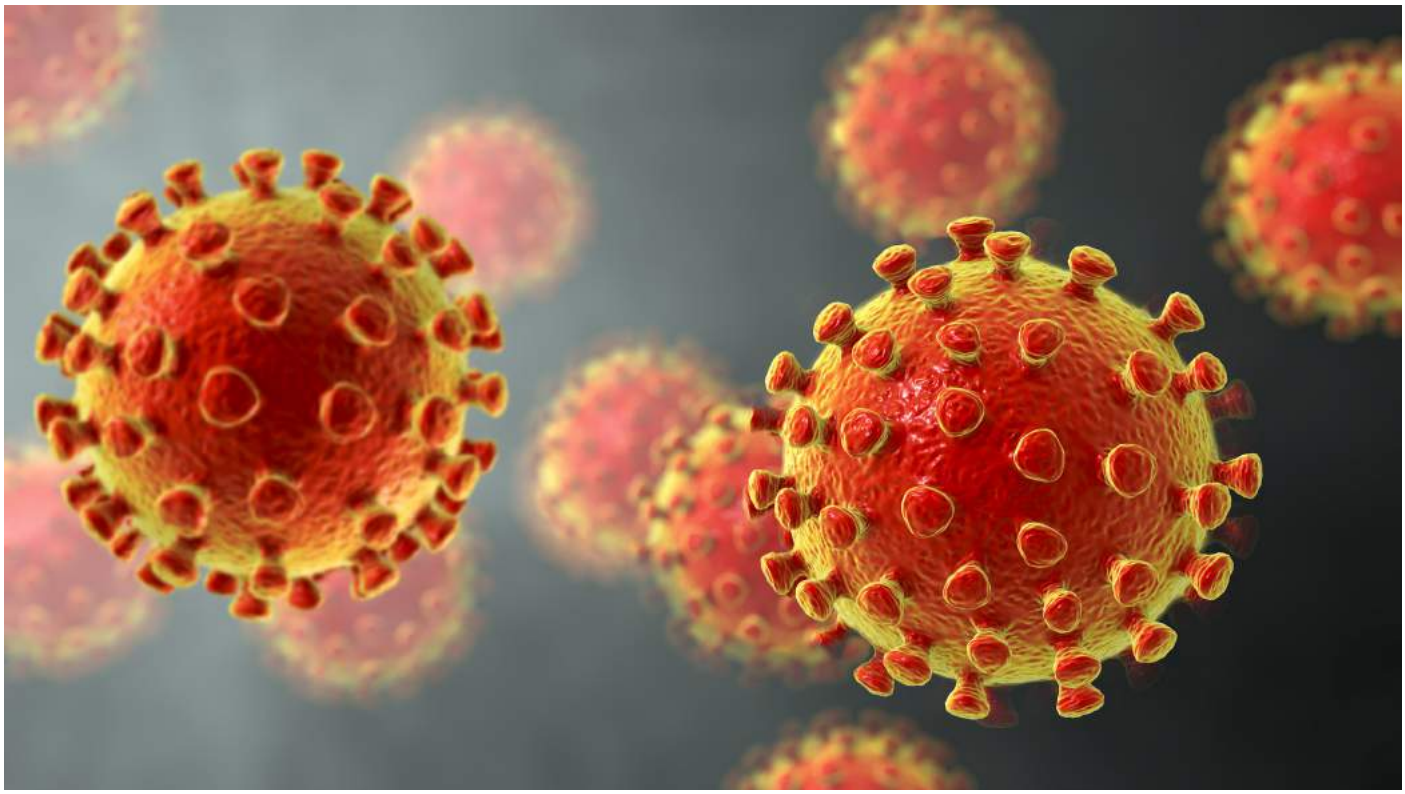
T cell peptide epitopes for reagents in COVID-19 testing

Researchers at the University of Oxford have identified a panel of T cell peptide epitopes specific to SARS-CoV-2.



COVID-19

The COVID-19 pandemic has had an unprecedented global effect since the novel coronavirus emerged in late 2019. COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Whilst the majority of cases are mild, a significant number of patients develop a severe illness linked to an overactive immune response and viral-induced pathology. Polymerase chain reaction (PCR) testing can identify patients currently infected with SARS-CoV-2 whilst antibody tests are being used to identify those that have recovered from the virus, including those who were asymptomatic.

Peptide epitopes specific to SARS-CoV-2

Researchers at the University of Oxford have identified a panel of over 70 T cell peptide epitopes that can be used as specific reagents in COVID-19 diagnostic tests. These peptides containing T-cell epitopes were derived from a cohort of COVID-19 patients and are specific to SARS-CoV-2, not other circulating coronaviruses.

They provide a tool to identify cases that may be missed in either PCR or antibody-based testing. The panel of peptides can be used in ELISPOT assays to identify early-stage infections before a patient develops symptoms and detectable levels of antibodies.

Additionally, using the peptides as reagents for the detection of T cells can identify patients that were previously infected and could be used to monitor vaccine-induced T cell responses. This test has the advantage of increased sensitivity over existing diagnostic methods as the panel of peptides is optimal for inducing T-cell responses.

Intellectual property protection

Oxford University Innovation has filed a priority patent covering this pool of peptides. We are seeking partners to help develop and expedite access to this diagnostic technology.

For further information please contact:

enquiries@innovation.ox.ac.uk
+44 (0)1865 280830
www.innovation.ox.ac.uk
Project number: 17993

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Optimising the performance and specificity of RT-LAMP based assays

Oxford University researchers have developed a colorimetric RT-LAMP assay with a temperature sensitive primer to enhance specificity of the reaction.

Loop-mediated isothermal amplification (LAMP) is a simple and rapid DNA amplification technique which is being used to detectpathogens such as virus, bacteria and malaria. LAMP reaction generally takes place in a constant temperature and the target DNA can be amplified in 30 min. The LAMP method employs - 6 primers binding to six regions of the target DNA. The use of six primers, recognising six distinct target sequences provides for a high degree of specificity and selectivity in LAMP methods, which is particularly important in diagnostic applications.

Nonetheless, several reports from other research groups have indicated that carryover contamination, the formation of primer-dimers and self-amplification can lead to false positives when conducting RT-LAMP assays.

Oxford's solution

The University of Oxford has developed an improved RT-LAMP with higher stability and reliability than the originals. The method uses a short oligonucleotide designed as a switch, which comprises a sequence that is complementary to a sequence encoded by one of the RT-LAMP reaction primers.

The oligonucleotide serves as a temperature-dependent switch to bind an essential primer of LAMP. When the temperature is lower than working temperature of LAMP, the switch binds the complementary primer and previent it from binding to the target DNA sequence, which in turn inhibits unspecific or off-target amplification.

At the working temperature, the switch dissociates from the corresponding primer, allowing it to bind target RNA/DNA for reverse transcription and subsequently the amplification of the target sequence.

The researchers have demonstrated that using this oligonucleotide switch to improve the stability and reliability of (RT-)LAMP is highly efficient. The incidence of false-postive results can be dramatically reducedcompared to the conventional LAMP.

Furthermore, the researchers have developed a vacuum-dried/freeze-dried master mix for single step RT-LAMP reaction, simplifying the operation for end users and easing long-term storage and transportation.

The new RT-LAMP assay has been applied and tested for testing RNA samples extracted from different clinical samples SARS-CoV-2 and shown high specificity. This improved, inexpensive and rapid colorimetric assay has considerable practical benefits over the current standard RT-qPCR assays and has great potential to be deployed in different diseases as a first-line screening tool.

Commercialisation

A patent application has been filed for the invention and is available for licensing.

For further information please contact:
Andrew Chan
andrew.chan@innovation.ox.ac.uk
+44 (0)1865 614422
www.innovation.ox.ac.uk
Project number: 17999

Technology Transfer from the University of Oxford

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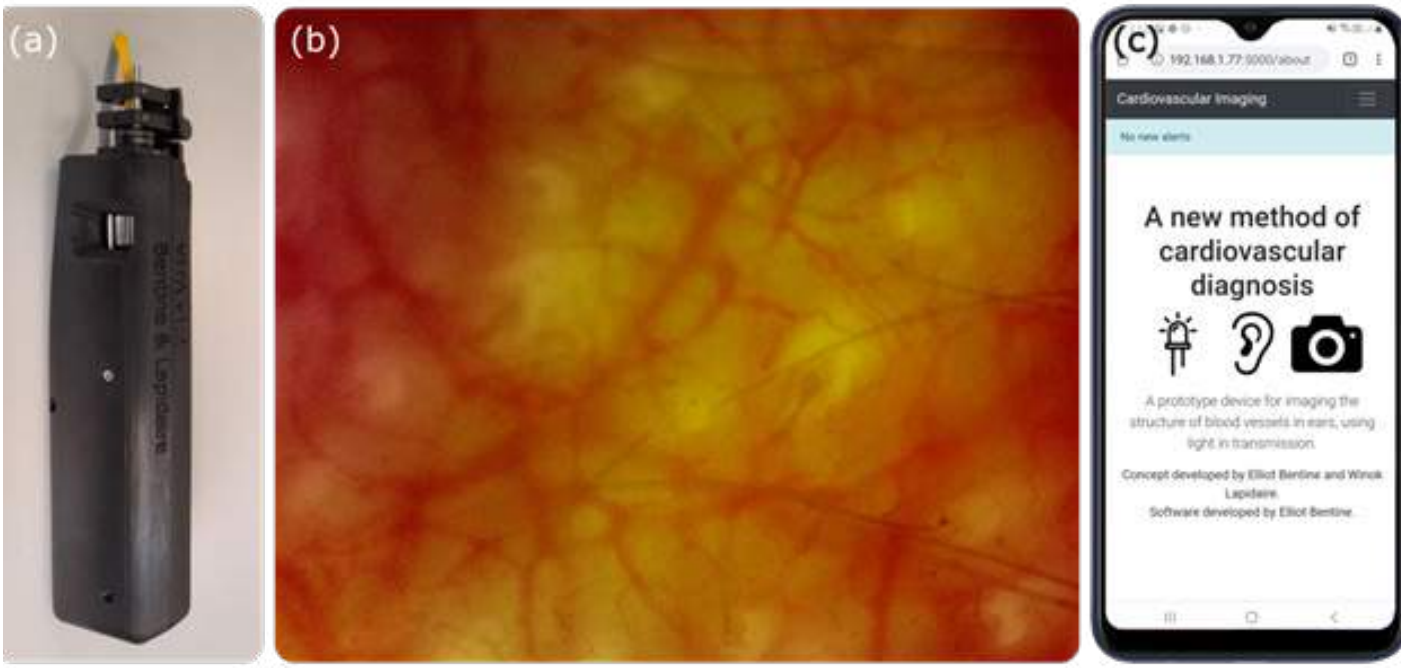
Portable imaging device for early detection of cardiovascular disease

Researchers at Oxford have developed a non-invasive device to detect, diagnose, and monitor cardiovascular disease by imaging the microvasculature.



(a) Hand-held VITA imaging tool (b) image taken with the VITA tool, showing small vessel structure in the ear, (c) WiFi connected user interface as seen from a smartphone.

Cardiovascular diseases (CVDs) are conditions of the heart and blood vessels, including strokes and heart attacks. CVDs are the leading cause of deaths globally and a major contributor to disability. It is estimated that CVDs caused over 17 million deaths in 2016.

CVDs are strongly linked to physiological and structural changes of the microvasculature, such as vessel size and branching. These alterations often precede major cardiovascular events and can be used as early diagnostic markers for CVDs. Early detection of these changes may lead to improved patient outcomes.

Detecting CVDs early

Commonly, retinal imaging or MRI are used to detect and diagnose CVDs. MRIs provide detailed imaging of the larger vessels and retinal imaging allows direct visualisation of the microvasculature in the eye. Although effective, these imaging methods can be expensive and time consuming. Furthermore, they are unsuitable for some patients; for example, they cannot be brought to the bedside.

By exploiting techniques from microscopy, optics and laser technology, Oxford scientists have developed VITA (Vasculature Imaging Tool for the Auricle), a portable device for imaging the ear vasculature.

This device functions by transmitting light through the ear, which allows a wide range of complementary imaging techniques to be used. These different techniques offer sensitivity to a range of disease biomarkers.

Imaging the ear also gives a range of practical advantages. The ear can withstand much brighter light than the eye which increases the image quality. Imaging the ear, rather than the retina, means that children or individuals that struggle to keep their eyes open can be easily examined.

The small design and smartphone compatibility allows the device to be portable and used in a range of settings.

For further information please contact:

enquiries@innovation.ox.ac.uk
+44 (0)1865 280830
www.innovation.ox.ac.uk
Project number: 18187

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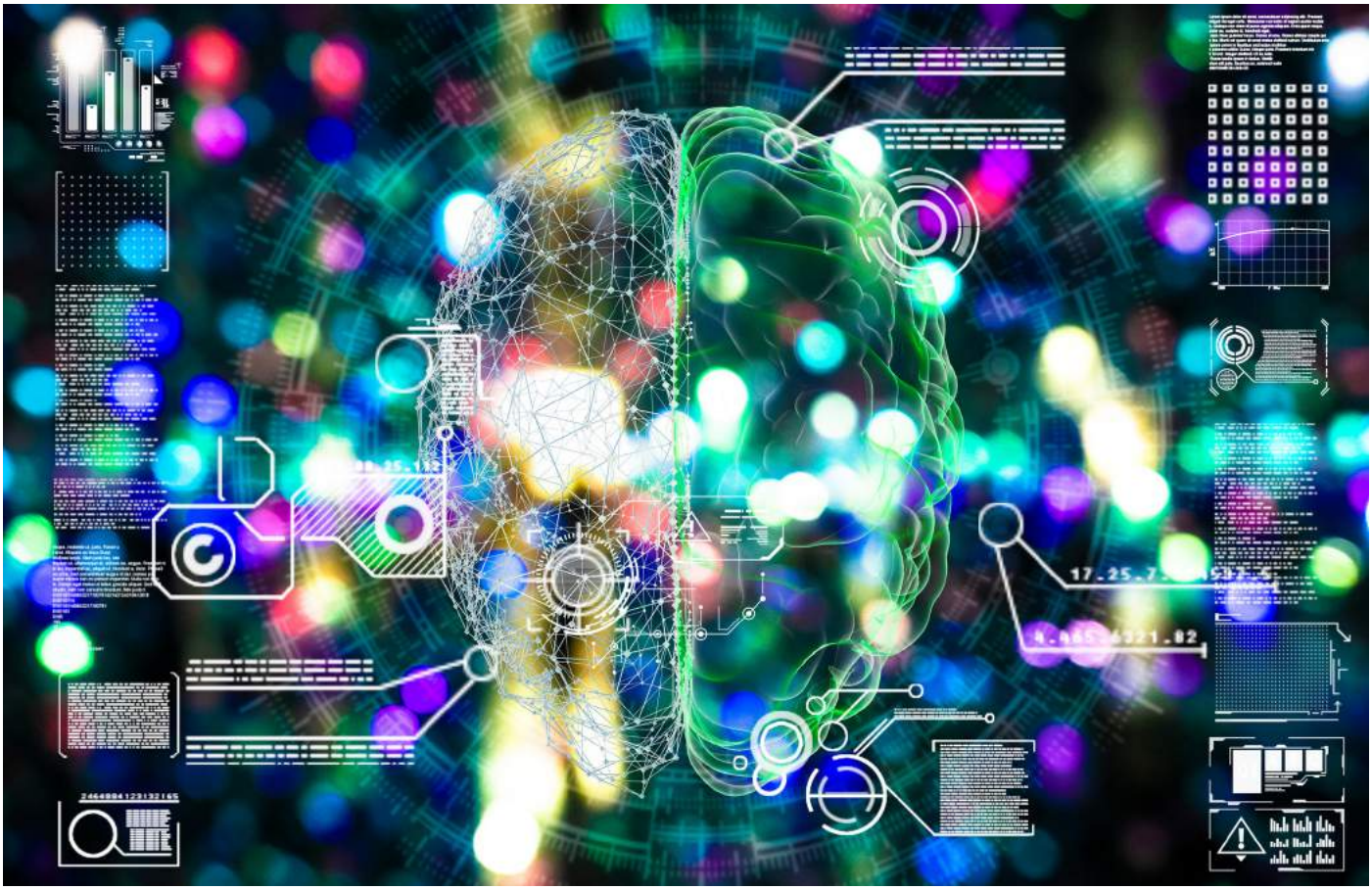
Federated meta-learning for healthcare applications

A new method, based on machine learning, for predicting patient's state in critical care.



Across the healthcare sector, a large amount of data is generated via medical health records, diagnostic and wearable devices and test results.

Data-driven machine learning continues to be a strong approach for collecting large volumes of medical data. However, the digitised healthcare data often contains sensitive information, and a data leak may compromise the patients' privacy. To avoid such scenarios, strict standards are in place to restrict access to sensitive healthcare records. As a result, collecting the distributed healthcare data at a third-party-owned centralised location to train machine learning models is not always feasible.

A large amount of healthcare data is generated every day but obtaining labels for this rapidly generating data is either unfeasible or highly resource-intensive. Hence, the amount of available labelled training data is significantly less than the unlabelled data.

As a result, unsupervised and semi-supervised machine learning methods have gained significant interest for many healthcare applications.

Scientists at the University of Oxford have developed a method in which a machine learning model is trained using a combination of federated learning, semi-supervised learning and meta-learning. This combination of features facilitates use of a large amount of decentralised healthcare data for semi-supervised multi-tasking while minimising the likelihood of data leakage.

For further information please contact:

enquiries@innovation.ox.ac.uk
+44 (0)1865 280830
www.innovation.ox.ac.uk
Project number: 18209

Technology Transfer from the University of Oxford

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Machine learning framework using physiological data

A supervised machine learning framework that can summarise the clinical state of a patient from physiological data.

The challenges of big data in healthcare

The continued growth of healthcare data is being digitised through new devices, apps and monitoring technologies. Such growth is driven by the digitisation of old patient records, the presence of novel monitoring systems, and the recent recommendation to improve the exchange of health records.

Healthcare data may include the results of tests and measurements carried out on individual patients. Physiological signals such as ECG signals convey a significant amount of information about the functionality and potential abnormalities of an individual's body, for example, their heart. Therefore, analysis of these increasingly available large datasets has the potential to provide various improvements in clinical practice.

Machine learning has been used toautomatically detect heart abnormalities, such as arrhythmias and has proven quite successful in recent years. However, diagnoses generated by these algorithms are applied to large datasets and remain population-based and are difficult to interpret.

Consequently, medical practitioners are reluctant to integrate network-generated predictions into their clinical workflow.

The potential for AI in healthcare

Scientists at the University of Oxford have developed a supervised machine learning framework that can learn representations, known as prototypes and can use these to summarise the clinical state of a patient using such physiological data. These prototypes have many functions; such as the ability to provide a compact representation of large datasets, identify patients that are similar to one another in a large dataset, clustering patients according to certain diseases and retrieve information on patients that belong to certain subgroups.

This information is particularly useful in a clinical setting because not only can it facilitate improvement in disease diagnosis but by retrieving patients that belong to certain clinical subgroups, it can help to facilitate the choice of cohorts in clinical trials.

Furthermore, the technology has particular application in the field of wearable sensors (such as wearable ECG devices) and digital health.

For further information please contact:

enquiries@innovation.ox.ac.uk
+44 (0)1865 280830
www.innovation.ox.ac.uk
Project number: 18210

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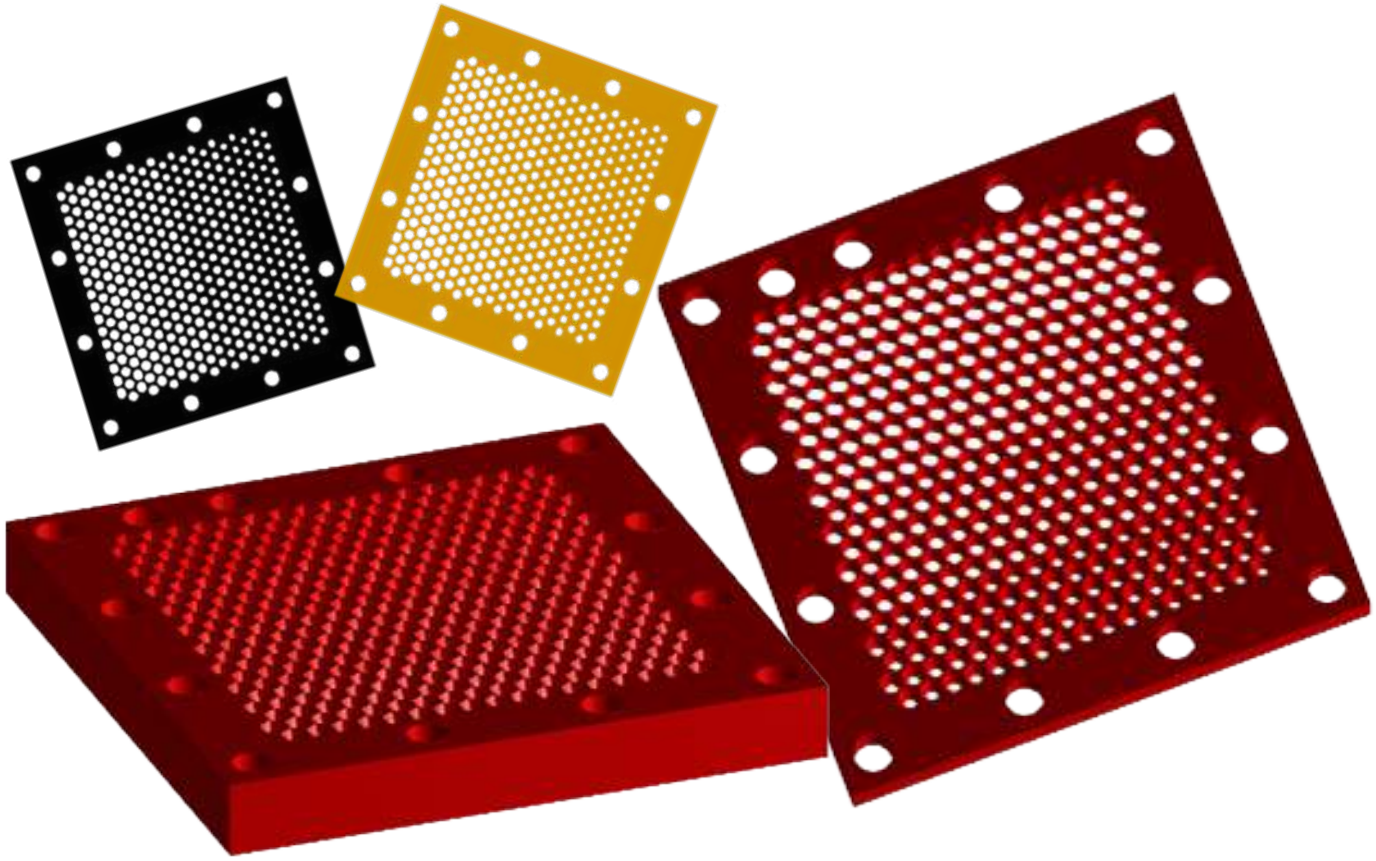
Shaping Sound: patient specific waveguide arrays for therapeutic ultrasound

Oxford scientists have developed a method for creating an array of acoustic waveguides to modify the phase and/or amplitude of transmitted sound.



Ultrasound is widely used for medical imaging and increasingly in therapeutic applications for example in the treatment of cancer. However, tissue inhomogeneity can affect the accuracy with which ultrasound can be focused in the body. This is particularly problematic in applications in which high intensity ultrasound is used.

One solution to this that has been implemented in a small number of commercial ultrasound systems is to use an array transducer to enable “steering” of the ultrasound beam. This approach, however, greatly increases the cost and complexity of the system and individual treatments. An alternative is to use patient-specific acoustic lenses that can be fitted to simpler ultrasound systems.

Scientists at the University of Oxford have developed an alternative to conventional acoustic lenses in the form of a grid of acoustic wave guides. The grids can be manufactured rapidly (< 1 hour) and at very low cost (<£20) and may be easily integrated into clinical ultrasound systems.

They offer efficient modulation of the phase and amplitude of the transmitted sound field, enabling the required exposure conditions within the target tissue.

The method may also be of interest for other applications where ultrasound lenses are used, such as for non-destructive testing, or underwater imaging.

For further information please contact:

enquiries@innovation.ox.ac.uk
+44 (0)1865 280830
www.innovation.ox.ac.uk
Project number: 18918

Technology Transfer from the University of Oxford

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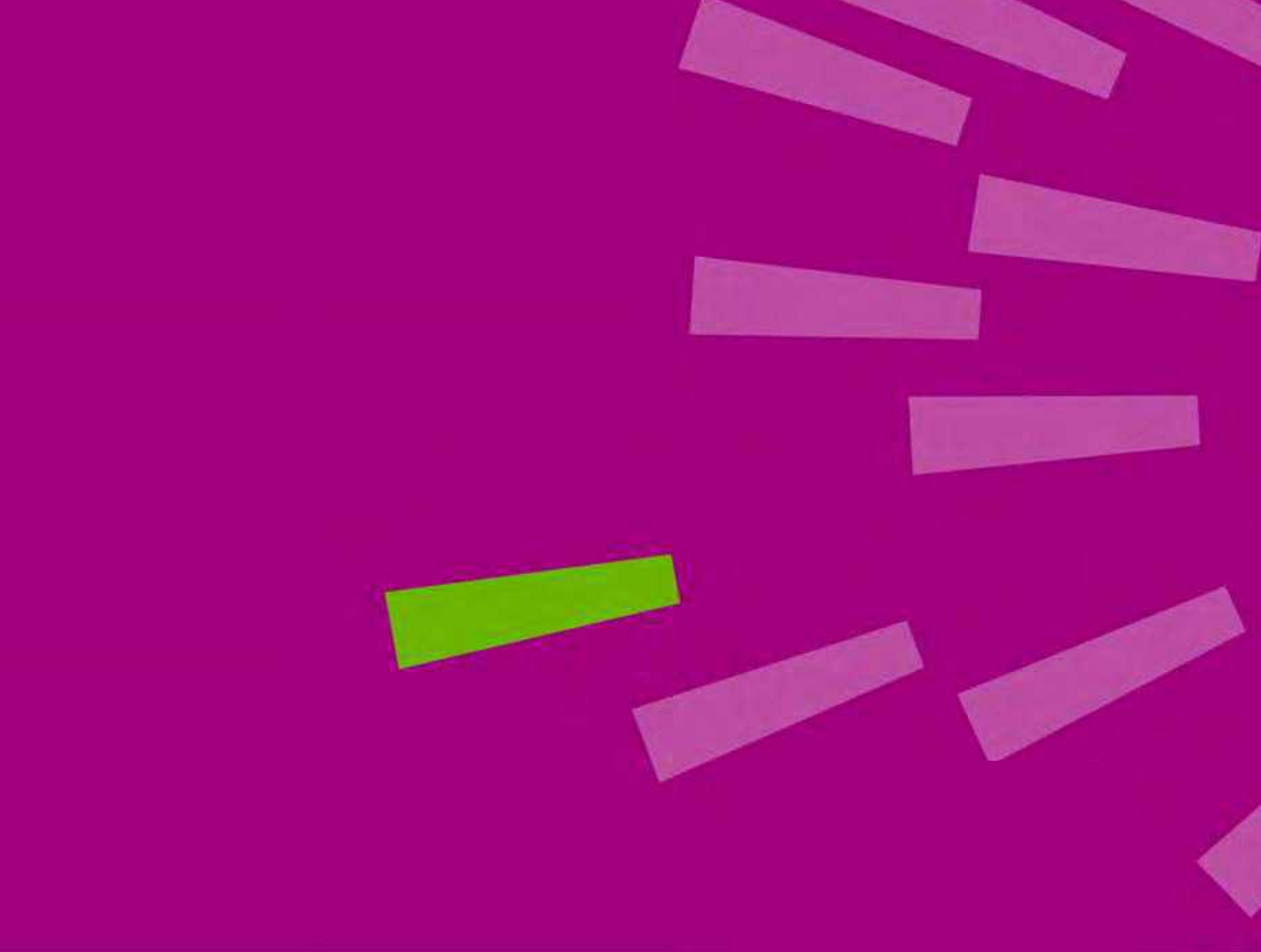
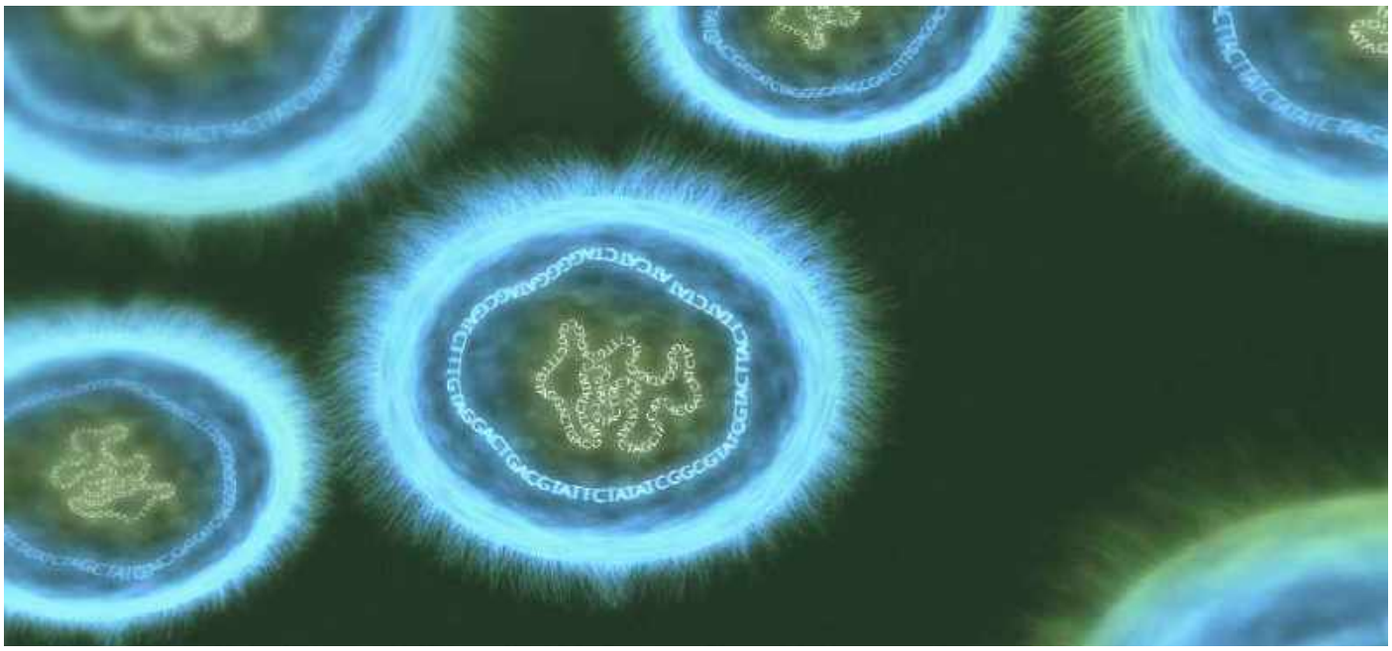


GENOMICS

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

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Chromopainter – Identifying shared ancestry

Available to license: An algorithm that analyses data from dense genotyping chips to infer local ancestry with high precision

Oxford researchers have developed an algorithm which can precisely identify stretches of DNA that are shared among individuals

Ancestral analysis

Tracing the genetic origin of a species can provide unprecedented insight into the history of a population. By comparing the DNA of individuals, genetic analyses can unearth information about the geographical and temporal ancestral relatives of an individual or group. This technology has wide ranging applications from disease mapping to understanding human history.

Analysis methods

Accurately identifying segments of DNA that individuals have inherited from different ancestral sources can be highly challenging.

Previous methods have used data that is too coarse, leading to ambiguous predictions, or they have failed to account for linkage disequilibrium, the connection between several allele at different loci, potentially resulting in misleading or incomplete inferences.

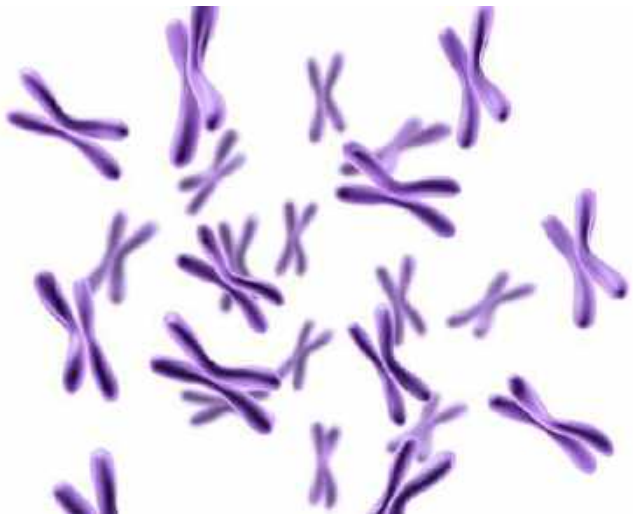
Chromopainter – Ancestry evolved

Oxford researchers have developed Chromopainter, an algorithm that analyses data from dense genotyping chips to infer local ancestry with very high precision. It is the most accurate tool of its kind as it makes use of key haplotypes, groups of genes that are inherited concurrently. These haplotype markers are known to be more informative than the simple use of individual loci. Simulations have demonstrated the ability of Chromopainter to uncover previously unknown aspects of population history.

The key benefits of the Chromopainter method are as follows:

- Analyses dense, large-scale diploid data from individuals with mixed ancestry
- More powerful than existing approaches at inferring ancestry
- Increased precision to distinguish between closely related ancestral sources
- Utilises haplotype information that many previous approaches ignore

The software is copyright protected and Oxford University Innovation Ltd wish to talk to companies who may be interested in using the Chromopainter algorithm.



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: 14061

Technology Transfer from the University of Oxford

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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

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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

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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

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Using the CHLORAD pathway to improve crop yield traits

Researchers at the University of Oxford have shown the Chloroplast-associated protein degradation (CHLORAD) pathway presents novel targets for manipulating crop yield traits.

Protein import is vital for chloroplast functioning

Plastids, including chloroplasts, are specialised organelles found within plant cells. Development and functioning of plastids is dependent on the import of thousands of proteins, carried out by TOC proteins located in the outer membrane and TIC proteins located in the inner membrane. The CHLORAD pathway influences plastid development by interacting with TIC/TOC proteins to modify protein import and degradation.

Impact of CHLORAD pathway manipulation

Stabilisation of TOC proteins, triggered through inactivation of the CHLORAD SP2 gene, results in alternations to plastid development. This can be applied to induce a “stay-green” phenotype through delaying conversion of chloroplasts into gerontoplasts, another type of plastid. Cereals exhibiting the “stay green” phenotype show an increased grain yield due to an extended photosynthetic period, and an additional benefit is a reduction in the development of pathogens which develop at the end of the growing season.

Mutants over expressing CHLORAD proteins also demonstrated an improved response to abiotic stress tolerance. This could be applied in crop species to reduce yield losses in response to abiotic stresses.

The CHLORAD pathway could also be targeted to influence fruit ripening. It has been demonstrated in tomato that fruit ripening can be accelerated through an increase in expression level of CHLORAD pathway genes causing a depletion of TOC proteins. Alternatively, fruit ripening could be delayed through inhibiting protein activity.

Market opportunities

The technology would be utilised in the creation of unique seed products with improved traits. Current estimates for the size of the global seed market range between $50-60 billion. According to Mordor Intelligence, this market is expected to increase with a CAGR of 7.1 % to 2022.

The gene editing market is demonstrating high levels of growth, expected to grow at a CAGR of 51.2% to 2022. In crops where GM approaches have not been adopted, such as wheat, gene editing represents a clear market opportunity.

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, 16172

Technology Transfer from the University of Oxford

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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

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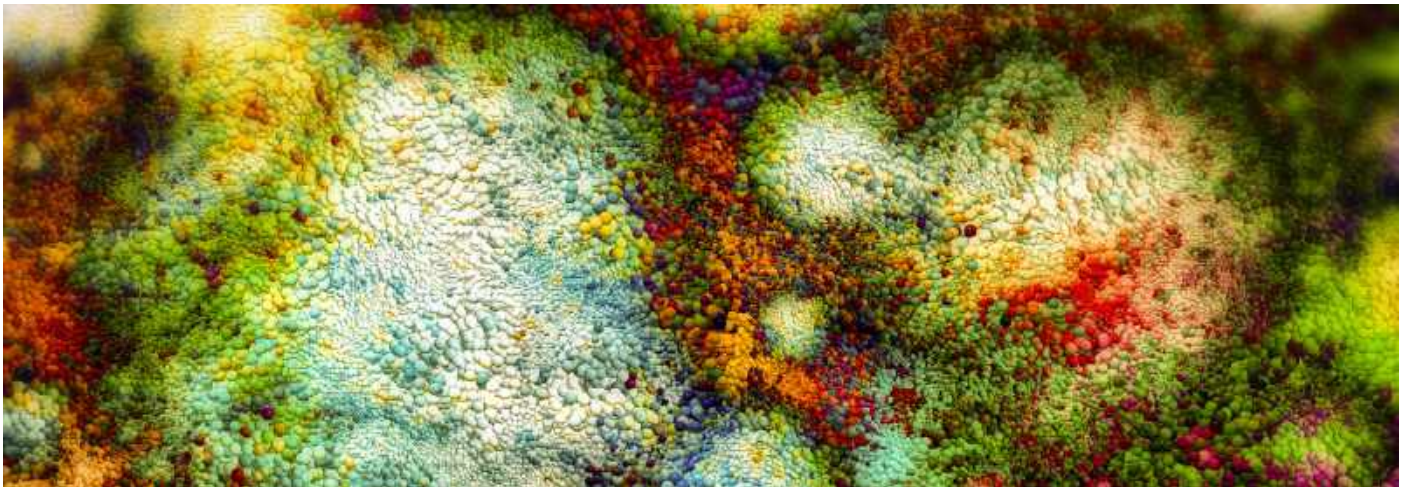
A method for genetic modification of biofilms

University of Oxford researchers have developed the application of ultrasonic cavitation to induce gene uptake by established biofilms.



Biofilms and microbial community - for better or worse

Biofilms are communities of microorganisms that cover a multitude of surfaces, in plant and animal tissue, underwater and above ground; wherever moisture is present, biofilms can form. From the plaque on your teeth, to breaking down contaminants, biofilms can be both very useful and harmful.

Modifying the genetic make-up of biofilms

The ability to modify the genetic make-up of biofilms directly where they are growing unlocks the potential for their enhancement or removal. Enhancing biofilm performance is particularly attractive in environmental clean-up, bioprocessing and biocatalysis where they are widely exploited. Gene modification of biofilms in situ also has potential in bio-manufacturing where introduction of new genes enabling novel properties, increasing yields and robustness is attractive. Similarly, adding DNA that would eradicate biofilm formation on implanted medical devices, such as pacemakers, or those that cause blockages in pipe-lines would improve safety and reduce energy demands. Another potential is implementing human microbiome therapies. The approach may enable problem bacteria such as Clostridium difficile to be modified, reducing pathogenicity, so reducing threat to the human microbiome.

The Oxford technology

The ability to directly modify genetic composition without compromising biofilm structure is key to their exploitation and to date approaches to achieve this have been limited. Microorganisms in biofilms are largely unculturable meaning standard methods of genetic modification are not feasible, since they require growth on laboratory media. Research in Department of Engineering Science has produced a methodology employing inertial cavitation to facilitate transformation of host cells with externally derived DNA. Employing ultrasound, the inertial cavitation enables DNA delivery into the cells through transient membrane disruption.

The DNA transformation of such organisms generates a wealth of potential across many markets including waste-water treatment, oil and gas, bio-manufacturing, human microbiome and is suitable for use with a variety of nucleic acids depending on the application. The technology can also be extended to deliver nucleic acids into mammalian cells.

Patent protection

Oxford University Innovation has filed a patent application 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 Philippa Christoforou
philippa.christoforou@innovation.ox.ac.uk
+44 (0)1865 280842
www.innovation.ox.ac.uk
Project number: 16224

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IMPUTE 5

Researchers at the University of Oxford have developed 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.

Genome-Wide Association

Genome-Wide Association (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 5 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 5 include:

- Algorithm based on use of Positional Burrows-Wheeler Transform (PBWT).
- Best in class performance. Up to 30x faster than MINIMAC4 and up to 3x faster than BEAGLE5.
- Can be used with large reference panels, such as the Haplotype Reference Consortium or TopMed datasets.

Oxford Genome-Wide Analysis Software Suite

IMPUTE 5 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 5 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: 16992

Technology Transfer from the University of Oxford

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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

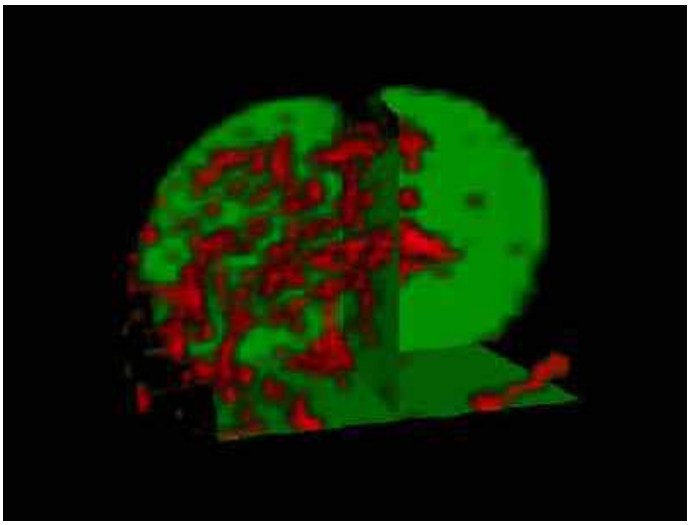
Brain metastasis is one of the greatest hurdles in cancer therapy; 20-40% of all cancer patients will suffer metastatic spread of primary cancer to the brain, and the prognosis is poor. Tumour cells use cellular adhesion molecules, normally associated with leukocyte trafficking, to metastase to non-CNS 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:
Andrew Bowen
andrew.bowen@innovation.ox.ac.uk
+44 (0)1865 614449
www.innovation.ox.ac.uk
Project number: 2924, 6596

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Improved inflammation imaging

Available to license: Lewis-sugar based MRI contrast agents

The new agents provide excellent diagnostic images for inflammatory diseases, enabling faster and more accurate diagnosis.

Imaging techniques – including MRI, PET and Ultrasound – are employed for the diagnosis and staging of disease. Contrast agents are used in imaging to increase the signal difference between the area of interest and background. Such agents can be divided into two general categories, those passive agents which non-specifically enhance the signal that is produced and targeted contrast agents which are chemically modified in order to localise to a specific cell type or tissue through an active mechanism. Passive agents are most widely used, but reflect downstream pathology.

Targeted agents, by contrast, can reveal the earliest of changes associated with disease development by virtue of their ability to recognise molecular changes in a particular cell or tissue that precede changes in tissue structure. Such targeted agents overcome the difficulties of high background signal in order to provide a clear picture for the clinician. There is a need for improved contrast agents that can be targeted to cell surface receptors to enhance imaging techniques.

Oxford invention

Oxford researchers have found that novel Lewis-type sugars can recognise and bind to activated endothelial cells *in vivo*. Furthermore, when conjugated to a suitable imaging moiety, e.g. an MRI-active material, the conjugate enables the activated endothelium to be visualised.

Benefits of this approach

Oxford researchers have used their invention to generate new imaging agents to diagnose diseases associated with endothelial activation including inflammatory diseases such as MS & atherosclerosis. The conspicuity of these conjugates is significantly improved compared with known passive or targeted imaging agents. The use of well-conserved sugars enables species boundaries to be easily crossed and these sugars are much easier to produce than previously used targeting moieties.

Patent protection and commercial opportunities

The underlying technology is the subject of an International Patent Application. There are several other complementary targeted imaging projects which have been developed at Oxford:

- Project 2468 , Sugar-targeted imaging agent
- Project 2924, Biodegradable multimeric iron oxide particles
- Project 6596, Humanised monoclonal antibodies to VCAM-1

Companies interested in progressing the commercial opportunities are invited to contact Oxford University Innovation.

For further information please contact:
Dr Emily Morris
emily.morris@innovation.ox.ac.uk
+44 (0)1865 614435
www.innovation.ox.ac.uk
Project number: 9030

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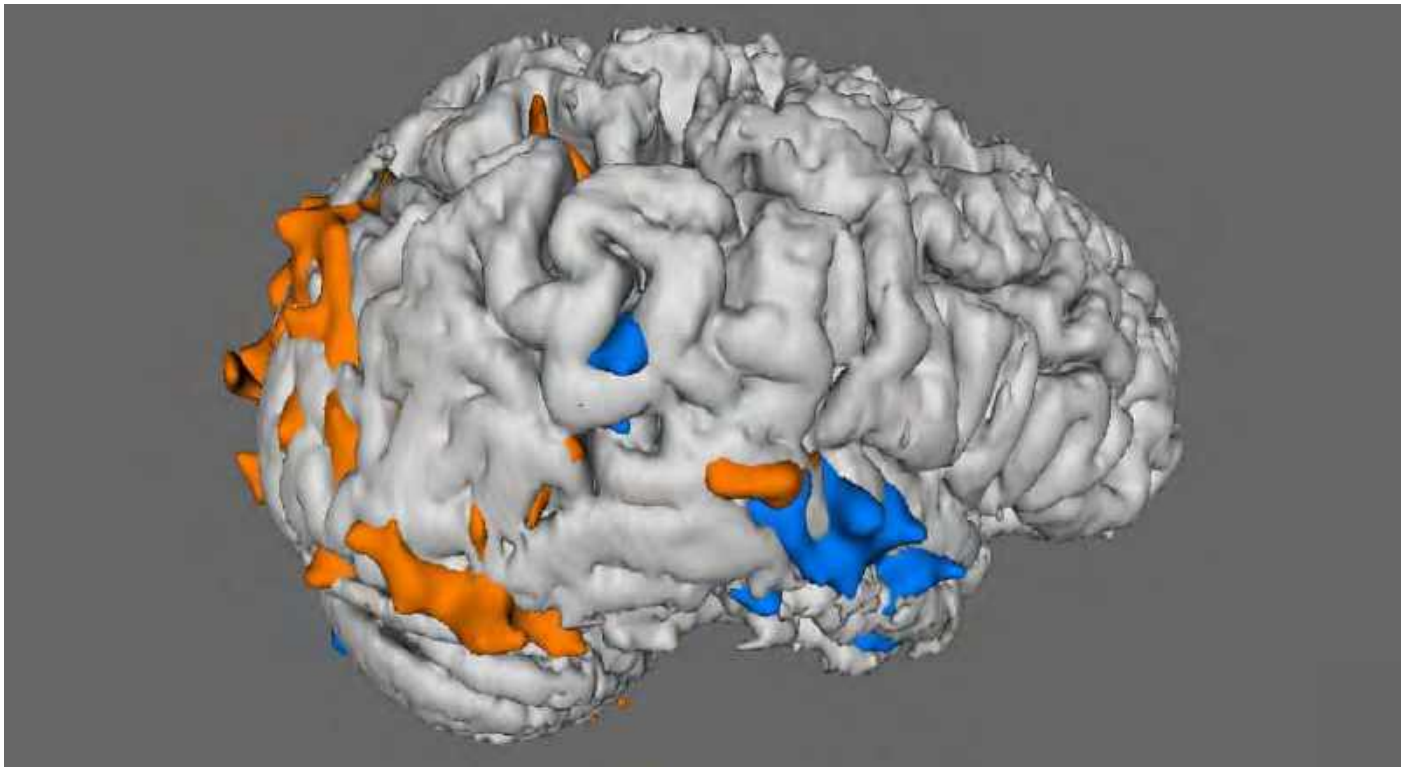
FSL brain-mapping software

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

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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

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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.

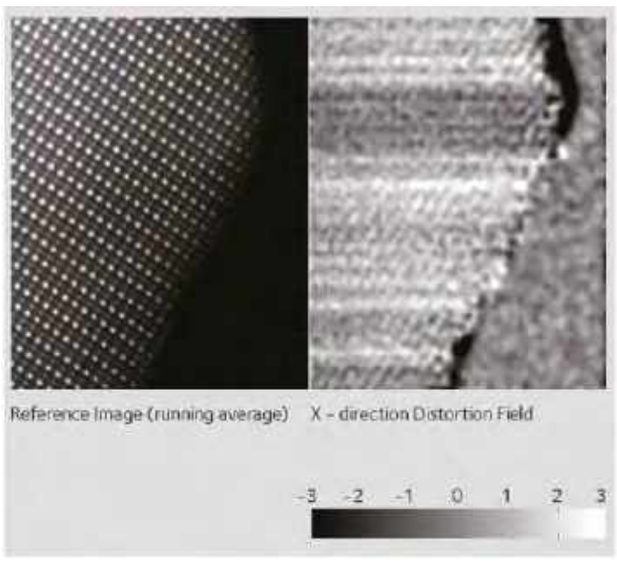
Demonstration available

'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

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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.

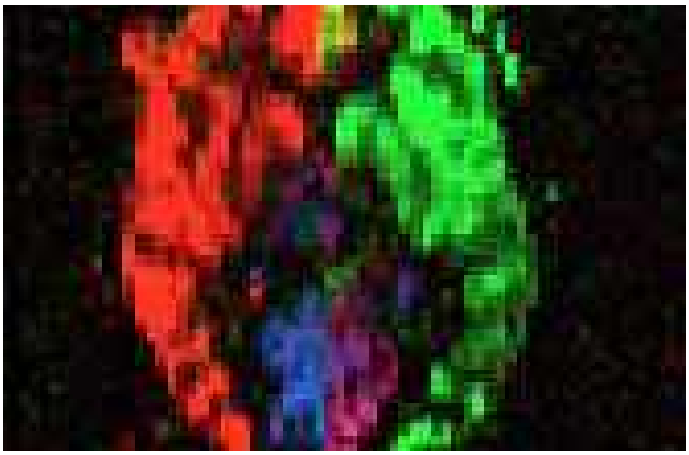
VEPCASL has an advantage over other vessel-selective methods in that it allows vessels to be labelled that are closer together. However, off-resonance (magnetic field inhomogeneity) in the labelling plane can occur in either case, leading to a reduction in labelling efficiency and thus image quality.

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

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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

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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

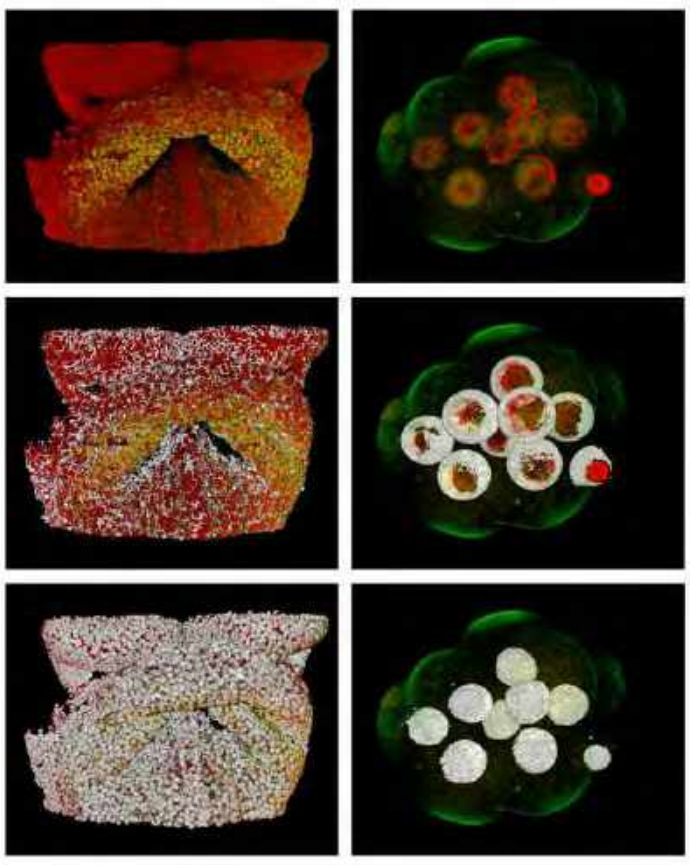
The proprietary University of Oxford platform has a graphical user interface and has been tested in the context of developing tissues where initially low cellular density geometrically simple structures transform into high cellular density geometrically complex structures.

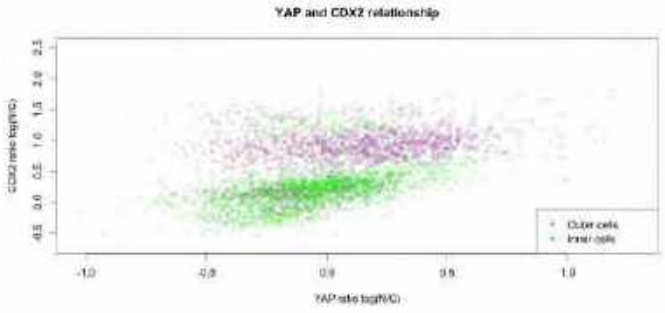
The tissues on which the software has been tested include mouse stem cell embryoid bodies and mouse cardiomyocytes during heart development, tissues comprising from 2 to an estimated 2,000 cells respectively.

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

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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.

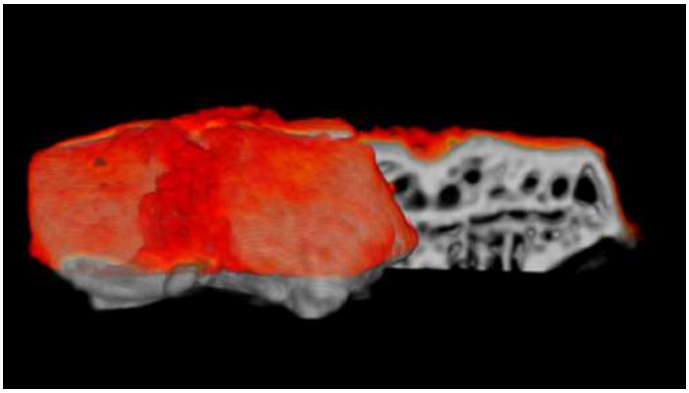
The technology provides:

- 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 614458
www.innovation.ox.ac.uk
Project number: 13952

Technology Transfer from the University of Oxford

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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

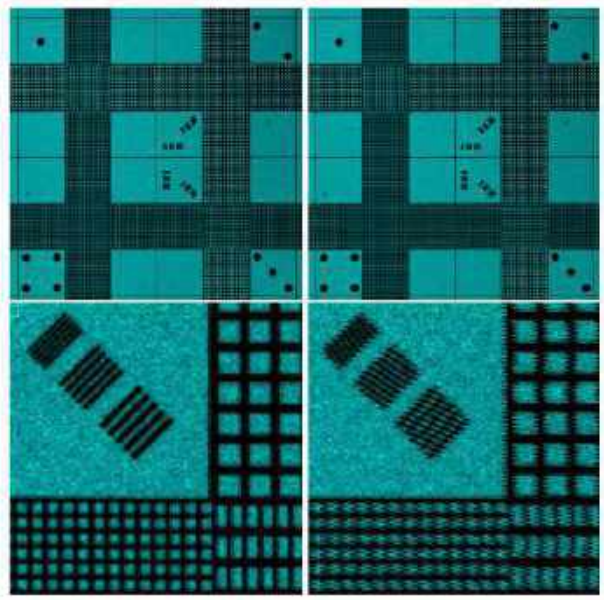

Image: (top left) Image obtained by unidirectional line acquisition, together with zoom (bottom left); (top right) image obtained for the bidirectional line acquisition together with zoom(bottom right). The image obtained by bidirectional line acquisition shows severe jaggedness artefacts for every second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

For further information please contact:

enquiries@innovation.ox.ac.uk
+44 (0)1865 280830
www.innovation.ox.ac.uk
Project number: 14289

Technology Transfer from the University of Oxford

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Non-invasive PET imaging of PARP expression

Oxford researchers have developed the first [^{18}F]-labelled olaparib, thus allowing *in-vitro* and *in-vivo* monitoring of olaparib accumulation in tumours.

PARP inhibitors in anticancer therapy

Tumorous tissues are characterised by having genomic instability due to replicative stress, external genotoxicity and DNA repair defects. The manipulation of such instability provides a therapeutic space in which inhibitors of DNA damage repair (DDR) enzymes have been studied as anti-cancer drugs. Poly (ADP-ribose) polymerase (PARP) are a class of DDR enzymes, and its inhibition has been the subject of numerous studies. The first clinically approved and most studied PARP inhibitor is olaparib (Lymparza®), currently present in a plethora of clinical trials focused on its use as a single drug, or in combination with chemo-, immuno-, or radiation therapy.

Despite the therapy being highly successful, resistance to PARP inhibition remains a current challenge when applying the therapy to patients. Among the causes, it was found that resistance is often due to low PARP enzyme expression. Consequently, methods to evaluate PARP expression status in tumours are critical; however, current approaches remain invasive and might not fully represent the heterogeneity of the sample.

Measurement of PARP expression

Positron emission tomography (PET) has become highly popular as an alternative method to measure PARP expression *in vivo*, as it allows for a non-invasive, whole-body and repeatable visualisation of olaparib delivery and binding to PARP. Several radiolabelled olaparib derivatives have been developed and applied in the understanding of DDR mechanism; however, their structural deviation from their parent molecule makes them unsuitable for further development.

[^{18}F]olaparib for PET imaging

Oxford researchers have applied their expertise on novel radiofluorination methods and synthesised the first [^{18}F]-labelled olaparib from a bench stable precursor. This “hot” compound has an identical structure to the unlabelled version meaning that better data can be gathered about the fate of olaparib *in vivo* compared to those labelled analogues which use large linker moieties or surrogates.

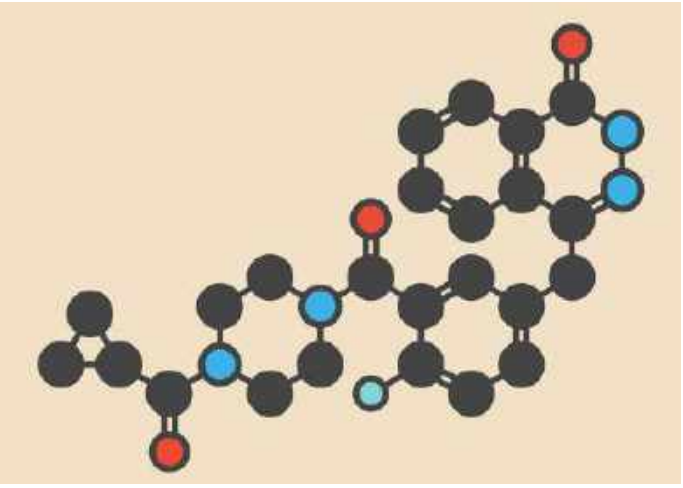
In vitro and *in vivo* translation of [^{18}F]olaparib includes:

- Dynamic monitoring of bio-distribution and uptake
- Pharmacokinetics and clearance patterns studies
- Measurement of PARP binding
- Detection and monitoring of DNA damage
- Study of the relationship between hypoxia and PARP expression

In summary, [^{18}F]olaparib was shown to be highly valuable in quantifying olaparib tumour accumulation both *in vitro* and *in vivo*, thus enforcing its translational use as a PARP imaging agent for clinical PET.

Protection and Applications

Oxford University Innovation is currently seeking a licensee to help commercialise the technology and has filed a UK priority patent application to protect this innovation.



For further information please contact:
Jane Jin
Jane.Jin@innovation.ox.ac.uk
+44 (0)1865 280846
www.innovation.ox.ac.uk
Project number: 15151

Technology Transfer from the University of Oxford

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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

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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.

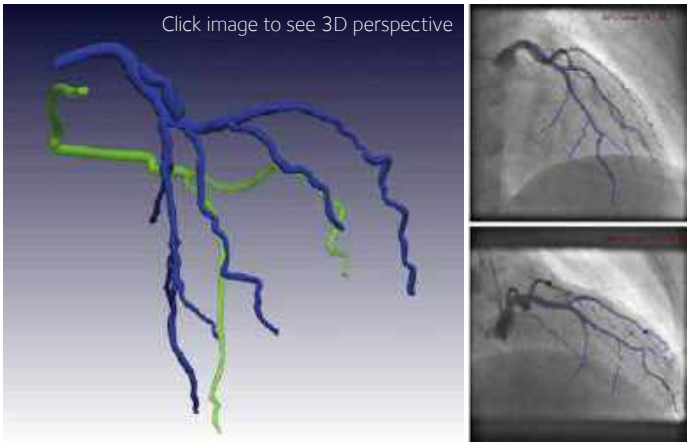
The Oxford solution

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

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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

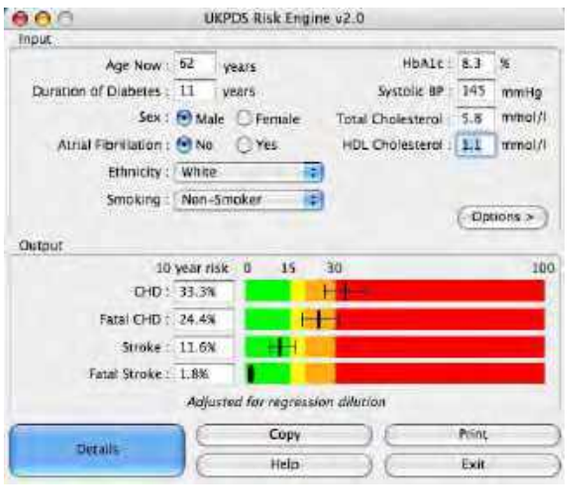
Applications

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:
Karl Dickinson
karl.dickinson@innovation.ox.ac.uk
+44 (0)7557 345975
www.innovation.ox.ac.uk
Project number: 8949

Technology Transfer from the University of Oxford

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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.

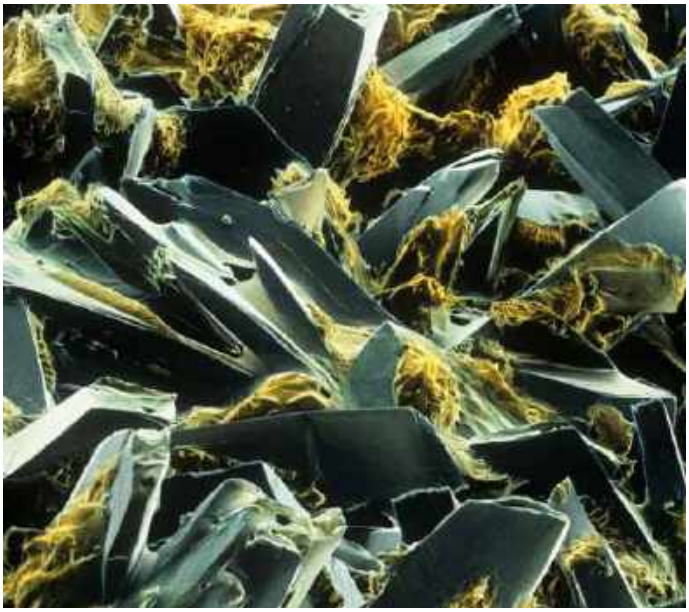

Image: False colour SEM of glucose crystals

For further information please contact:
Karl Dickinson
karl.dickinson@innovation.ox.ac.uk
+44 (0)7557 345975
www.innovation.ox.ac.uk
Project number: 9797

Technology Transfer from the University of Oxford

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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:
Karl Dickinson
karl.dickinson@innovation.ox.ac.uk
+44 (0)7557 345975
www.innovation.ox.ac.uk
Project number: 9965

Technology Transfer from the University of Oxford

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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

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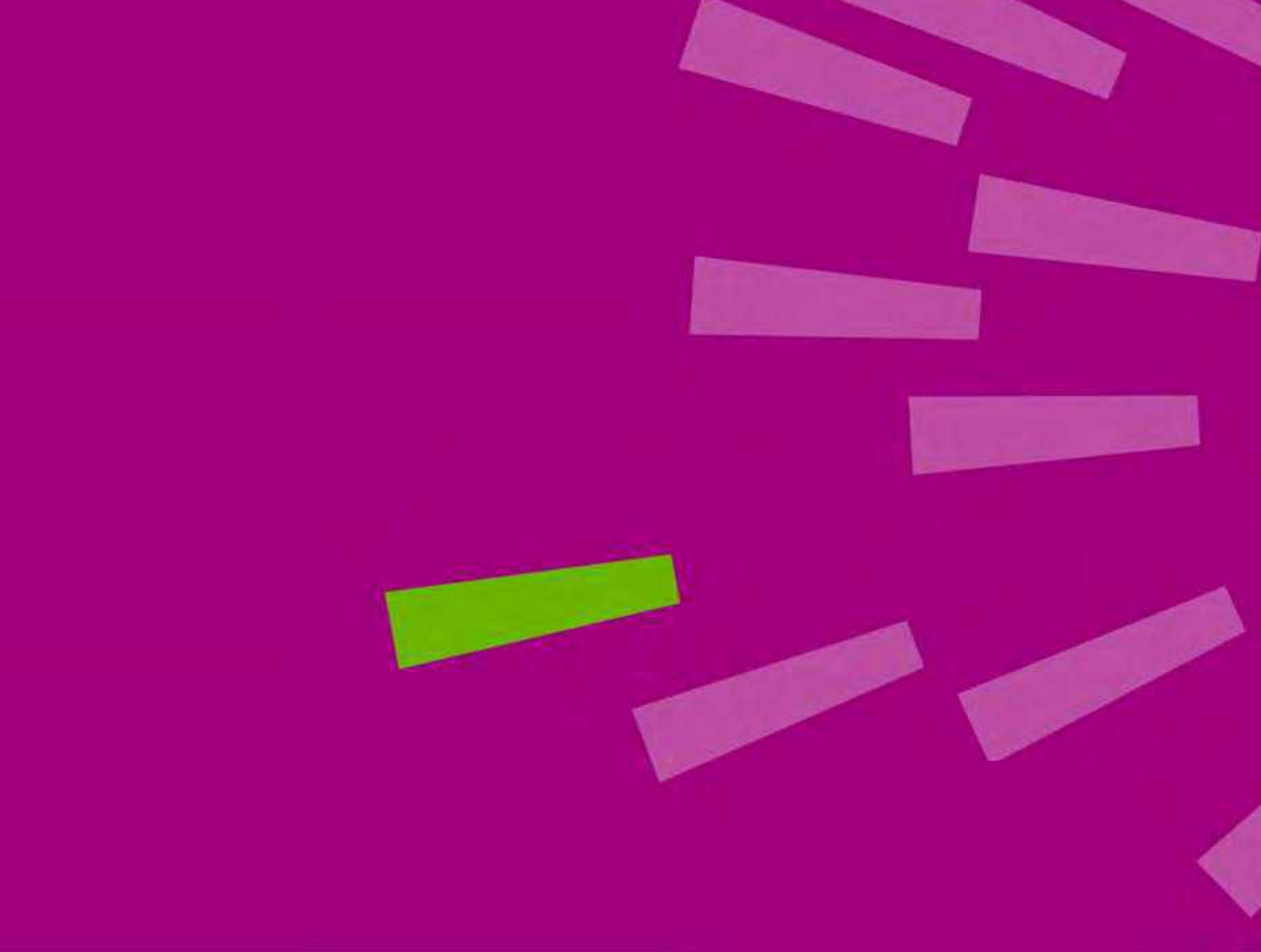

NEUROSCIENCE

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 Dinali de Silva
dinali.desilva@innovation.ox.ac.uk
+44 (0)1865 614441
www.innovation.ox.ac.uk
Project number: 8818

Technology Transfer from the University of Oxford

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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.

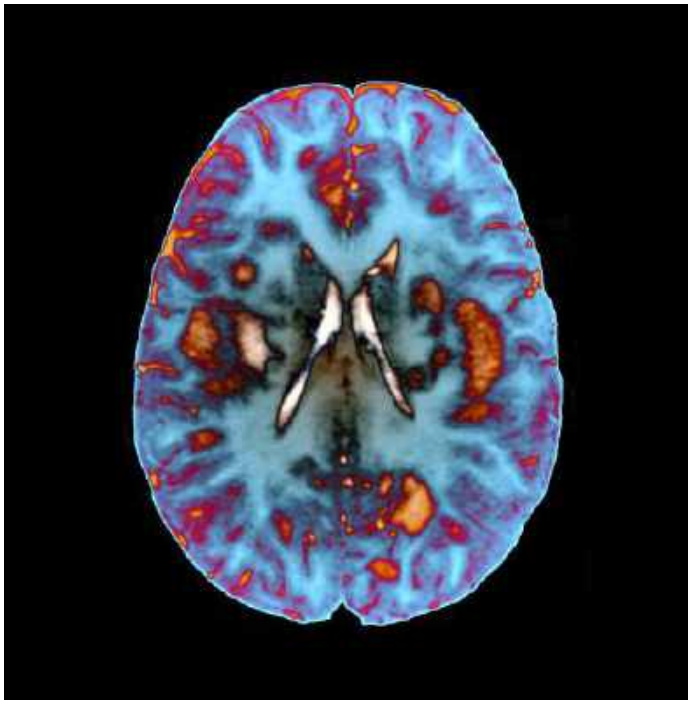
By retrospectively analysing the sera of patients suffering from a range of neurological and psychiatric symptoms, researchers from the University of Oxford have identified the α1 and y2 subunits of the $GABA_A$ receptor as a target of autoimmunity (published in the journal Neurology, Pettingill et al., 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:
Benedicte Menn
benedicte.menn@innovation.ox.ac.uk
+44 (0)1865 280906
www.innovation.ox.ac.uk
Project number: 11128

Technology Transfer from the University of Oxford

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Using inorganic nitrites as a marker for brain injuries caused by a stroke

Oxford researchers have developed a method to measure the brain response to nitrites as a biomarker of acute brain injury.

Following an acute brain injury like subarachnoid haemorrhage (a type of stroke), the brain continues to undergo secondary damage due to processes initiated by the primary injury ("early brain injury").

The main clinical priority following hospital admission is therefore to prevent the development of further brain damage. However, the extent and evolution of this secondary brain damage cannot easily be determined from currently available investigations.

Methods to quantify early brain injury in patients either depend on invasive monitoring (with risk of further brain damage) or the subjective and qualitative assessment of radiological images. Furthermore, standard bedside monitoring techniques require long recording periods to give useful clinical information. This results in difficulty guiding treatment and predicting neurological outcomes.

Clinical scientists at the University of Oxford have developed a method to measure the response of injured brain tissue to nitrites using bedside cerebral monitoring as a biomarker of neurological injury. The present invention takes a dynamic approach and tests the acute physiological response of injured brain tissue to a molecular probe. Such an approach allows diagnostically important and personalised information to be obtained in much shorter time scales, e.g. in the order of hours and minutes rather than days.

In particular, these biomarkers can give clinicians a valuable insight into which patients are most likely to develop further brain damage and, therefore, who would benefit from early intervention.

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: 12768

Technology Transfer from the University of Oxford

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Artefact-free recording for neuromodulation devices

Researchers at Oxford University have developed an efficient and easy-to-implement approach for simultaneous stimulation and artefact-free electrophysiological recording for advanced closed-loop neural modulation.

The need to close the loop during neural modulation

Deep brain stimulation (DBS) is a surgical procedure to implant a pulse generator under the skin to send electrical signals to brain areas responsible for body movement. It is effective in the treatment of many neurological disorders and could benefit millions of patients worldwide.

But its current clinical use is based on continuous stimulation (cDBS) which causes side effects and limits therapeutic benefit. There is considerable interest in developing “closed-loop” DBS devices capable of modulating stimulation in response to sensed brain feedback signals.

Limitations of current systems

Using electrophysiological signals recorded close to the stimulation target as a feedback signal has the advantage of cost effectiveness, since the same implanted electrodes can be used for both stimulation and recording.

However, the stimulation generates high voltage artefacts in the recording that can be up to a million times larger than the useful signal and degrades signal quality due to widespread signal contamination.

These problems remain the main technical challenges in developing more sophisticated and efficient closed-loop neuromodulation strategies. It also limits our understanding on how stimulation changes neural activities.

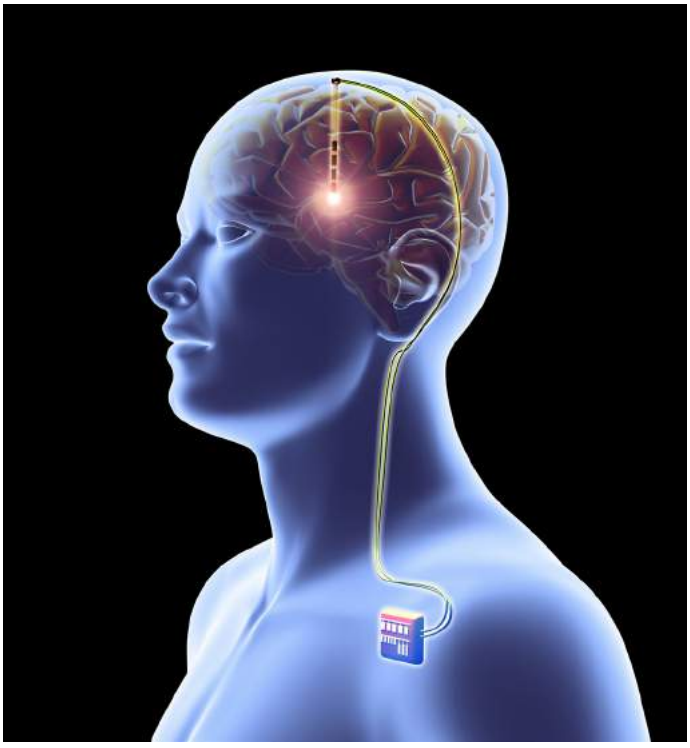
Simultaneous stimulation and recording for intelligent neuromodulation

Oxford academics and clinicians have developed a new technique for sequencing the recording of electrophysiological signals and delivering stimulation pulses.

This achieves true artefact-free recording during simultaneous stimulation. The technique significantly improves signal quality, so that the recorded activity can provide a rich source of feedback signals. This technique, validated *in vitro and in vivo*, is easily implemented as hardware or software on new or existing stimulation and recording systems.

Commercialisation

This technology is subject to a patent application. Oxford University Innovation is interested to hear from companies that would like to license this technology.



For further information please contact:

enquiries@innovation.ox.ac.uk
+44 (0)1865 280830
www.innovation.ox.ac.uk
Project number: 15499

Technology Transfer from the University of Oxford

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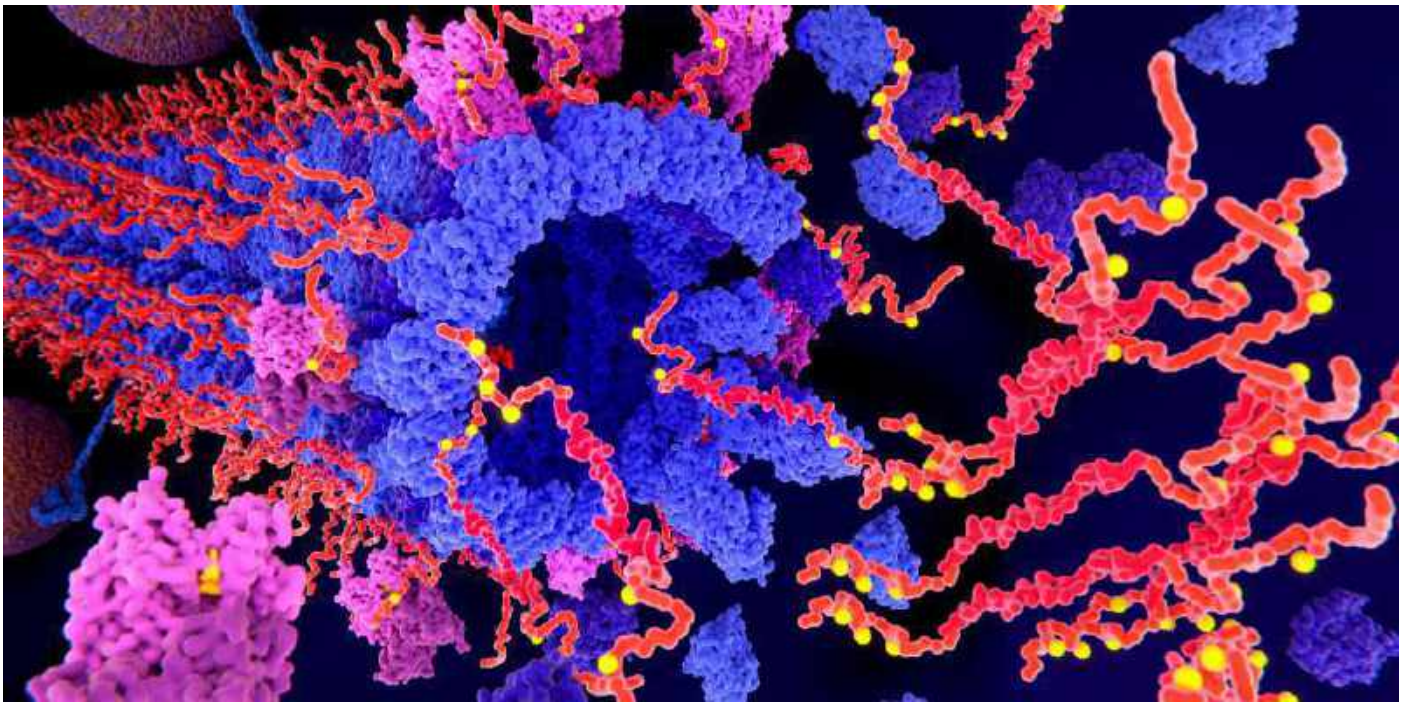
Targeted drug delivery to the brain for treating neurodegenerative diseases

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.

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Technology Transfer from the University of Oxford

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An all-optical associative learning element

Oxford researchers have developed an all-optical element which can mimic the associative learning process of humans and animals.

The interaction between humans and the environment and its impact on cognitive development has long been an inspiration in the development of autonomous systems and artificial intelligence (AI). Ian Pavlov's classic experiment nearly one hundred years ago demonstrated the power of this type of learning through showing how dogs can be trained to associate a bell with food (the output being salivation). In recent years, there has been a drive to replicate such associative learning or 'classical conditioning' in the development of AI and machine learning technology.

Neuromorphic engineering, also known as neuromorphic computing, relates to the concept of using electronic circuitry to mimic neuro-biological architectures present within a human or animal nervous system. From a hardware perspective, the basic elements of neuromorphic computing, i.e., artificial neurons and synapses, have been devised. However, these elements do not form single-element associations but instead require an ensemble of such elements to associate between datasets, thus increasing the computational and energy requirements.

A new approach to all-optical associative learning

Building on previous work focussed towards developing an all-optical neuromorphic computer, researchers at the University of Oxford have devised an associative learning element. Such an element can be integrated with existing neuromorphic computing components to create circuitry which can receive inputs, capture associations and output reactions analogous to Pavlov's dog experiment.

In this optical design, two complementary optical 'sensor (input) neurons' are embedded in two optical couplers. Energy (light pulses) from both couplers can be converged in an 'optical motor neurone' to determine when associations should be made. Simultaneous light pulses passing through each sensor neuron trigger a response in the 'motor neuron'. This leads to different output behaviour of the motor neuron to capture the fact that an association has been made previously. When desirable, the learning element can be reset ready to 'learn' future associations.

Unlike existing software, the all-optical associative learning element developed at Oxford is completely embedded in simple hardware, which provides unprecedented design flexibility and scalability for future neuromorphic computers.

Commercialisation

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.

For further information please contact:
Rachel Grovenor
rachel.grovenor@innovation.ox.ac.uk
+44 (0) 7551 372293
www.innovation.ox.ac.uk
Project number: 16759

Technology Transfer from the University of Oxford

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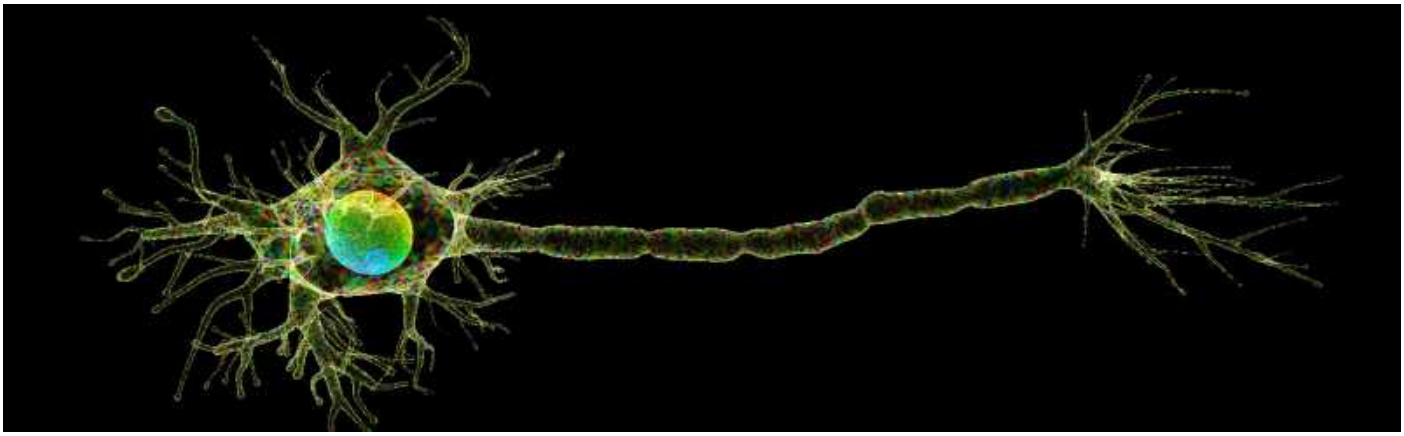
Amyotrophic lateral sclerosis diagnostic

Oxford University researchers have developed a ground-breaking technology for the early diagnosis of amyotrophic lateral sclerosis and other proteinopathy.



TDP-43 proteinopathy and ALS

TDP-43 protein is the neuropathological hallmark in 97% of Amyotrophic Lateral SclerosisALS, 50% of frontotemporal dementia (FTD) cases. It is also found in patients diagnosed with Alzheimer's disease (AD), a recently sub-classified 'limbic-predominant age-related TDP-43 encephalopathy' (LATE), which may have a different pathophysiology to classical AD and different symptoms.

All are untreatable neurodegenerative diseases and are a challenge to diagnose pre-symptomatically, precluding the development of preventative strategies. Individual neurodegenerative diseases represent the common end-stage of a variety of upstream pathological pathways that will require precision medicine based around key molecular pathways. In the case of ALS and FTD, a large body of evidence implicates TDP-43 dysfunction as the core pathogenic pathway, so that its reliable detection would have fundamental roles in diagnosis, stratification, and as a pharmacodynamic biomarker.

The neuropathological characteristics of TDP-43 proteinopathy in ALS and FTD are nuclear to cytoplasmic mislocalisation, post-translational modifications such as ubiquitination and phosphorylation, aggregation and importantly N-Terminal truncation of TDP-43 resulting in smaller C-terminal TDP-43 fragments.

Problem(s) addressed

ALS is primarily diagnosed based on detailed history of the symptoms and signs observed by a physician during a physical examination and a series of tests over a period. Measuring pathological TDP-43 by antibody-based ELISA has been unreliable so far and results often contradictory, most likely because of the lower amountsof pathological TDP-43 present in a complex matrix such as biofluids, and more importantly the commercially available TDP-43 antibodies are non-specific to disease-specific forms of TDP-43/ pathological TDP-43 and bind other proteins such as immunoglobulins. Specific antibodies that selectively bind disease-specifice and brain-derived TDP-43 and/or a definitive diagnostic test are not available in the current clinical setting.

Oxford's solution

To address this problem, researchers from the University of Oxford have developed technology for the absolute quantification of TDP-43 and its truncated isoforms by an antibody-independent technique. By determining the ratio between specific C- and N-Terminal TDP-43 peptides, which has been found specifically increase in ALS, discrimination of ALS from other neurodegenerative diseases becomes possible. Patients will be benefit from the definitive diagnosis and better management of the disease, that will subsequently reduce the burden of our health care system.

A sensitive and reliable assay for pathological TDP-43, which has been designated one of the top priorities for facilitating therapeutic advances in ALS and FTD. It will also be important in any future personalized medicine approach to AD therapy.

Commercialisation

A patent application has been filed for the invention; the technology is available for licensing.

For further information please contact:
Andrew Chan
andrew.chan@innovation.ox.ac.uk
+44 (0)1865 614422
www.innovation.ox.ac.uk
Project number: 16952

Technology Transfer from the University of Oxford

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Serum neuronal exosomes to improve early Parkinson's disease diagnostic

Researchers at the University of Oxford have developed a new immunocapture assay and identified biomarkers to predict and better stratify Parkinson's disease.

Parkinson's disease (PD) is the second most common neurogenerative disorder in the world affecting an estimated 7 million people globally. Its global prevalence is expected to double over the next 20 years, partly due to our increasingly ageing population. PD is caused by α-synuclein (α-syn) accumulation and aggregation inside neurons, especially dopamine-producing neurons, causing their death. It is typically preceded by a long prodromal phase, where individuals do not fulfil diagnostic criteria for PD but start to exhibit non-motor symptoms such as a sleep disorder called REM sleep behavioural disorder (RBD).

Early PD diagnostic remains challenging

Currently PD is diagnosed once a decline in motor symptoms has been recognised, with no single diagnostically conclusive test. By the time PD has progressed to the point whereby motor symptom deterioration is visible, up to 70% of dopamine neurons may have been lost. Additionally, the non-specific nature of the symptoms observed in early diagnosis results in PD often being missed or misdiagnosed. The development of efficient methods to assay key biomarkers in the earliest stages of PD will undoubtedly underpin therapeutic intervention when disease-modifying therapies become available.

α-synuclein is a promising PD biomarker

Current methods to measure α-syn concentration in patients biological fluids are either not efficient or not suitable in most clinical settings because this protein is produced by various cell types including red blood cells. An alternative approach is to quantify the concentration of α-syn released from neuronal tissues, such as neuron-derived exosomes, but the isolation of exosome subpopulations in complex biological fluids remains as of today challenging.

Efficient isolation of exosomes from contaminants

Researchers and clinicians at the University of Oxford have developed a new immunocapture assay which efficiently isolates exosomes from patients' serum.

Using this assay, they established that release of neuronal exosome-associated α-syn is an early pathophysiological response before the clinical diagnosis of PD. When used in combination with the levels of clusterin in neuronally-derived exosomes, PD and subjects with RBD who are at risk of developing PD could be distinguished from controls or patients with atypical Parkinsonism. This technology was tested and validated in a cross-sectional study of 735 patients from four independent cohorts.

Commercialisation

Oxford University Innovation is looking to hear from parties interested in developing or licensing this technology.

This invention is the subject of two patent applications (PCT/GB2020/052872 and PCT/GB2020/052871).

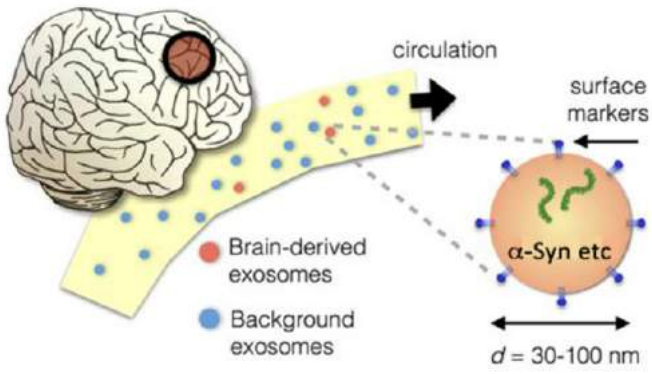

Image: Schematic representation of neuronal exosome isolation using anti-L1CAM conjugated zwitterionic polymer-modified magnetic beads.

For further information please contact:

enquiries@innovation.ox.ac.uk
+44 (0)1865 280830
www.innovation.ox.ac.uk
Project number: 16965

Technology Transfer from the University of Oxford

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A potential new therapeutic target for Parkinson's Disease

Researchers at Oxford have found a new target in the nicotinic cholinergic systems for the treatment of Parkinson's Disease.

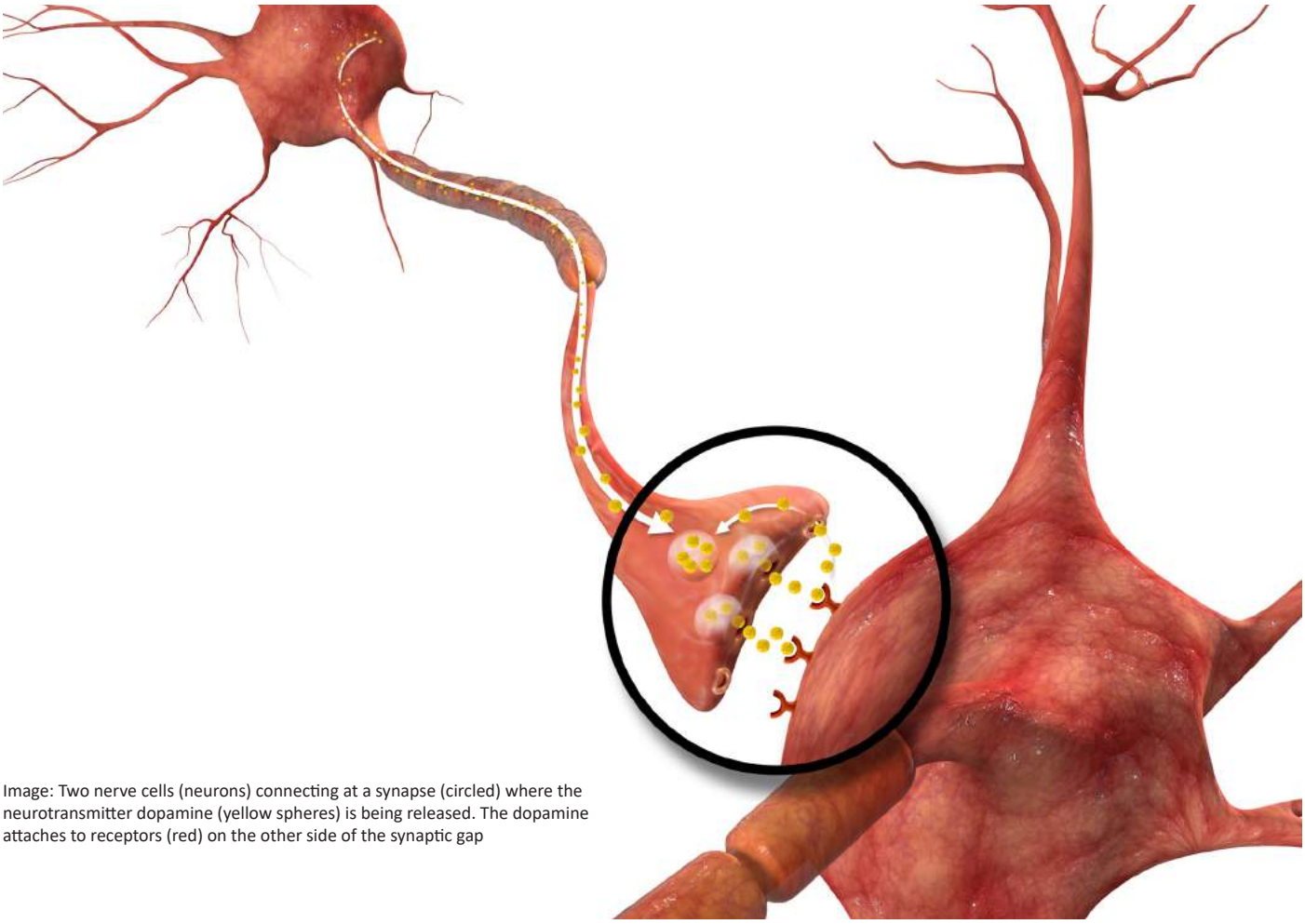

Image: Two nerve cells (neurons) connecting at a synapse (circled) where the neurotransmitter dopamine (yellow spheres) is being released. The dopamine attaches to receptors (red) on the other side of the synaptic gap

Treatments and therapies for Parkinson's Disease

Parkinson's Disease is associated with ageing and is caused by the loss of dopaminergic neurons in the midbrain. Current treatments, such as levodopa, work by increasing dopamine levels in patients to alleviate the tremors. However, such treatments can cause general elevation of dopamine levels in the striatum, including via the release of inappropriate non-dopaminergic inputs.

It has been reported in the journal *Nature* that long-term administration of this drug will increase the incidence of disabling motor side effects, known as levodopa-induced dyskinesia. Therefore, alternative therapeutic approaches are needed to reduce the side effects associated with levodopa.

New Parkinson's Disease treatment

Researchers at the University of Oxford have discovered that striatal cholinergic interneurons can successfully, and strongly inhibit dopamine release in the striatum by activating nicotinic acetylcholine receptors (nAChRs), including β2-subunit-containing nAChRs on dopamine neurons.

The administration of an nAChR antagonist/blocker can reverse the inhibition of dopamine release specifically caused by striatal cholinergic interneurons, thereby providing effective treatment for a condition or disorder in which reduced levels of dopamine are implicated, such as Parkinson's Disease. Such specificity effectively reduces the unwanted side effects caused by existing levodopa treatment.

Licensing opportunities

A patent application of this invention has been filed and it is available for licensing.

For further information please contact:

enquiries@innovation.ox.ac.uk
+44 (0)1865 280830
www.innovation.ox.ac.uk
Project number: 17514

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A combined diagnostic approach to identify patients with CASPR2 autoantibodies

A combined serological and genetic diagnostic algorithm to improve patient stratification of those suffering from rare neurological disorders.

Current serological CASPR2 autoantibody detection alone is not sufficient to determine patients responsive to treatment with immunotherapy

Patients with CASPR2 autoantibodies display a widespectrum of neurological symptoms such as neuromyotonia, Morvan's syndrome, various forms of encephalopathy, recognised pain disorders and forms of epilepsy.

Currently, immunotherapy is the gold standard treatment when a patient tests positive for CASPR2 autoantibodies. However, it is recognised that a number of patients with CASPR2 autoantibodies do not have immune-mediated neurological disorders and immunotherapy will not be effective in these cases.

Furthermore, commercially available tests to detect CASPR2-autoantibodies in the serum and cerebrospinal fluid of patients generates significant background noise in these assays. This makes a significant proportion of results uninterpretable which can lead to patients receiving the wrong diagnosis and unnecessary immunotherapy. In turn, the resulting side effects and harm of misdiagnosis often create additional and misleading problems for both clinicians and patients.

Hence, there is a need to improve specificity and this issue also applies to other antibody-associated conditions in neurology.

An improved, combinatorial diagnostic approach

Oxford academics have developed a combined serological and genetic algorithmic testing approach which improves the specificity of the assay for CASPR2-antibody associated diseases for cases which respond to immunotherapies. This reduces results which are clinically irrelevant and offers biological insights.

The first stage analyses the CASPR2 autoantibodies using a live cell based serological assay. A deeper analysis of the CASPR2 autoantibodies, determining the antibody titre and the specific subclass of the autoantibodies, provides clinicians with more accurate information about the patient's specific disease profile.

The second stage of the analysis is a genetic test, to identify if patients are carriers of a specific HLA allele. This specific HLA allele has been associated with the development of autoimmune neurological disorders mediated by CASPR2 autoantibodies.

Improving patient care

Small-scale tests of the diagnostic methods were able to accurately assess which patients with CASPR2 autoantibodies were likely to respond best to immunotherapy. Furthermore, these observations continue to be valuable in prospective patient care. The new diagnostic process will enable clinicians to rapidly identify the correct methods of treatment for patients with CASPR2 autoantibodies, saving time and money for healthcare providers, and reducing side effects for patients.

Commercialisation

Oxford University Innovation has filed a priority patent, PCT/GB2019/051257, covering this improved diagnostic approach. We are seeking partners to help develop 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: 15728

Technology Transfer from the University of Oxford

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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 Susan Campbell
susan.campbell@innovation.ox.ac.uk
+44 (0)1865 280872
www.innovation.ox.ac.uk
Project number: 4130, 11532

Technology Transfer from the University of Oxford

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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.

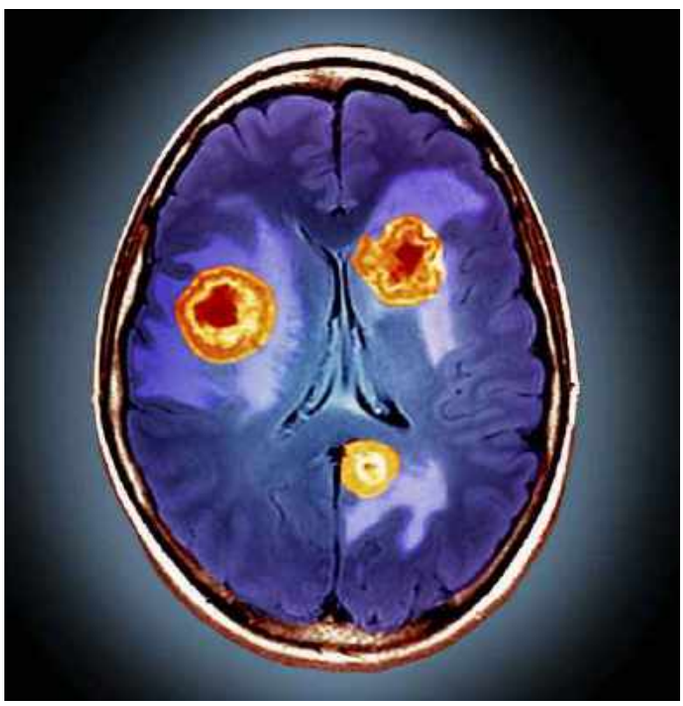
Supporting Data

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

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Rapid, cost-effective test for T cell lymphoma and leukaemia

Available to license: A novel test to diagnose lymphomatous and leukaemic T-cell infiltrates.

Researchers at Oxford have developed a novel method to probe the constant regions of the T-cell receptor beta chains in order to characterise the nature of T-cell infiltrates in tissues or in blood.

An approach to diagnose T-cell populations

Researchers at Oxford have developed a technology that offers a cheaper, quicker, simpler diagnostic test to distinguish benign and malignant T-cell populations.

Identification of lymphocytic and leukaemic cells in benign and malignant conditions

The differentiation between benign and malignant (eg lymphomatous or leukaemic) infiltrates is an important and common clinico-pathological question in routine healthcare practice.

While this is possible for B-cell infiltrates using kappa/ lambda immunoglobulin light chain staining, there is not an equivalent for T-cell infiltrates which currently require expensive and time consuming T-cell receptor gene rearrangement PCR studies to be undertaken, which are only possible in regional specialist centres.

We know that alpha-beta T-cells express either beta constant region 1 or beta constant region 2 in roughly equal proportions, and we now use this knowledge to develop a diagnostic test for routine histopathological practice.

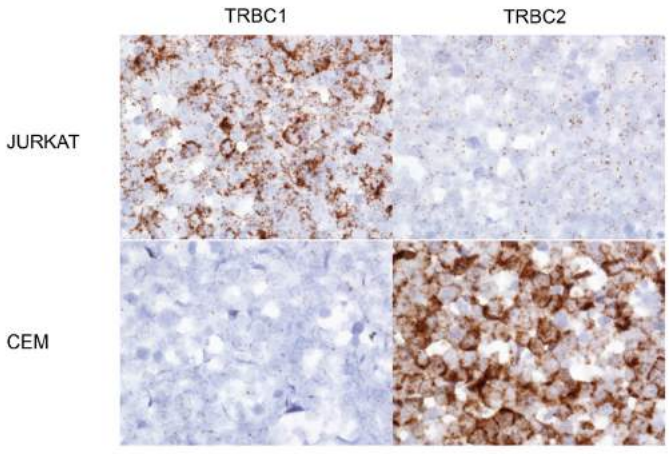
We believe the test will be invaluable in distinguishing benign and malignant (lymphomatous/leukaemic) T-cell infiltrates in tissue samples from sites including lymph node, bone marrow, intestine and skin. If successful, the test will have the potential to transform the routine assessment of T-cell infiltrates, and make it a rapid, cost-effective and widely available approach.

It is therefore likely to impact on international diagnostic guidelines with global health economic implications as this approach offers a cheaper, quicker, simpler diagnostic test to assess T-cell populations.

Ready for license

The technology is protected by a granted European patent. International patent applications have been filed and are under prosecution in the United States and China.

Our intention is to licence the IP to the appropriate partner whilst working collaboratively to develop an automated diagnostic test for routine histopathological practice. This would facilitate industrial access to relevant patient samples and clinical/ pathological expertise.



Mutually exclusive expression in T-cell lymphoma/ leukaemia lines, correlating with RT-PCR data.

For further information please contact:

enquiries@innovation.ox.ac.uk
+44 (0)1865 280830
www.innovation.ox.ac.uk
Project number: 7261

Technology Transfer from the University of Oxford

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Novel cancer treatment to improve the efficiency of radiotherapeutic methods

Oxford researchers have developed a new method to treat cancer by increasing the efficiency of radiotherapeutic techniques such as proton beam therapy and x-ray radiation.

A number of different techniques may be used in the management and treatment of cancers. These include chemotherapeutic methods, radiotherapeutic methods, photodynamic therapy, surgical methods, hormonal therapy and embolisation. Embolisation, in particular, is a non-surgical, minimally invasive procedure in which blood vessels are selectively occluded by introducing emboli. In cancer treatments, embolic particles can be introduced in to the blood stream close to the target and lodge in the small vessels which feed the tumour restricting blood flow. As a result, oxygen and nutrient supplies to the tumour are reduced which causes tumour necrosis.

Radiotherapeutic methods and photodynamic therapy are also effective in reducing tumour size. Photodynamic therapy (PDT) is commonly used to treat some types of cancer. PDT involves injecting a photosensitizing agent into the bloodstream of a patient. The agent is absorbed by cells all over the body, but it generally accumulates in the tumour due to abnormalities or defects in the tumour vasculature. It is also rapidly absorbed by cancer cells, which tend to grow and divide much more quickly than healthy cells and hence have a higher metabolic activity.

Cancers may also be treated using radiotherapy, which involves the use of ionising radiation, such as x-rays or proton beam radiation. Radiation therapy most commonly uses x-rays but protons or other forms of energy can also be used. Proton beam therapy is a type of radiotherapy that uses a beam of high energy protons rather than x-rays to treat specific types of cancer.

Scientists at Oxford have developed a method of improving the efficacy of cancer treatment by developing a range of embolisation particles to be used in conjunction with x-ray or proton beam radiation.

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: 9086

Technology Transfer from the University of Oxford

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Method to detect the Water Equivalent Path Length (WEPL) in proton CT therapy

Oxford University researchers have developed an alternative and less complex method using beam characteristics detected by a generalised 2D detector.

Proton therapy treatment

Proton therapy has the potential of being a paradigm shifting treatment modality for cancer. This is due to a physical property of heavier charged particles, which can come to a complete stop in a medium depositing the majority of their energy at the end of their track (Bragg peak). For a given energy of the particle and given medium, the range of such a particle is well known to within a few millimetres. This knowledge can be harnessed to produce dose distributions that spare normal tissue better than classical photon–based treatments.

Anatomical uncertainties

There is an increasing number of proton therapy facilities, but anatomical and setup uncertainties are currently hampering the effectiveness of therapy. Current approaches to address this issue include using transmission and CT imaging to determine errors, prompt gamma detectors and TOF PET, and methods to directly measure residual ranges.

However, this can require complex, expensive and large detector setups, which are challenging for clinical use.

Machine learning to determine WEPL

Researchers at the University of Oxford have developed an alternative and less complex method of inferring the Water Equivalent Path Length (WEPL) map, by analysing the beam characteristics detected by a generalised 2D detector placed beyond the patient.

Measuring WEPL in a patient can provide valuable information about how the treatment is progressing. This does not require reconstruction of each single particle path within the patient. The method involves the use of indirect data and the combination of parameters using machine learning to determine the WEPL of the proton beam inside the patient.

This method could be used to remove unnecessary complex equipment, enable targeting of a proton beam within a patient, and provide information on the accuracy and safety of the delivered treatment.

Commercialisation

Oxford University Innovation has filed a patent application on this method and is interested in speaking to companies who would like to licence the technology.

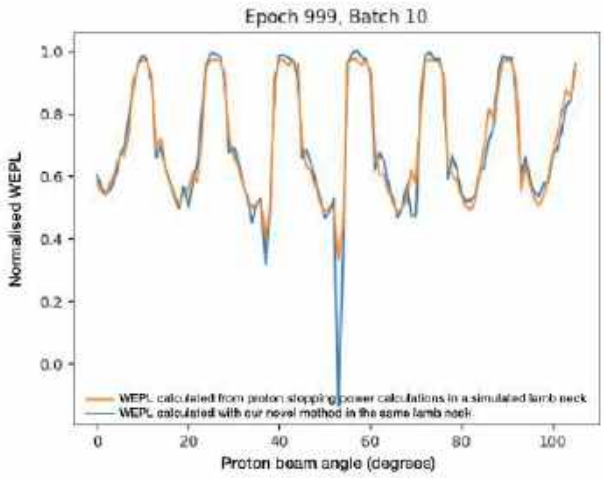

Fig. 1: After 1000 iterations the WEPL calculated with our novel method converges to the values of WEPL from conventional proton stopping power calculations obtained from a Monte Carlo simulations of a lamb neck CT.

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: 15395

Technology Transfer from the University of Oxford

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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.

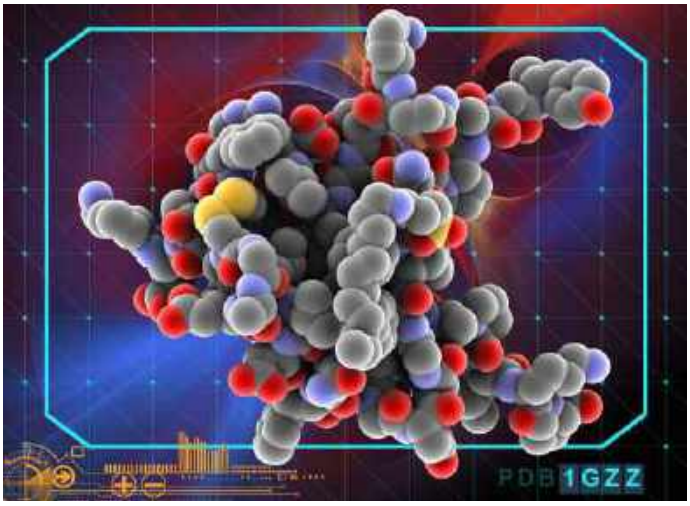
Inhibition of IGF signalling has been an area of major focus by pharma, with many failures due to either receptor redundancy (between IGF1R and IR-A) or the IGF1 feedback loop. This causes the pituitary gland to produce more growth hormone, instructing the liver to produce more IGF1, generating a potential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

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A biomarker to classify colorectal cancer patients

Oxford researchers have developed a biomarker for irinotecan-based chemotherapies for patients with metastatic colorectal cancer.

According to the World Health Organisation, colorectal cancer is the third most common cancer to affect both men and women and the third-leading cause of cancer-related death with 1.8 million new cases and almost 861,000 deaths in 2018. Developed countries are at the highest risk of colorectal cancers.

The number of biomarkers to indicate how patients will respond to a particular drug is very low. In particular, there is an unmet need for novel biomarkers that can facilitate the implementation of more targeted therapeutic strategies in cancer patients to improve overall clinical outcomes.

It is highly advantageous to identify a biomarker that can be used to isolate identify cancer patients that will or will not respond to particular treatments, for example to a TOP1 inhibitor, such as irinotecan. This will allow patients to be given the most appropriate treatment quickly and avoid administering treatment which will not be effective and/or has an undesirable side effects. Not only are there benefits to the patient, but it is clear that there will also be significant cost savings in identifying and selecting therapy-responsive patients.

Currently, chemotherapy remains a major first line treatment for advanced and metastatic colorectal cancer, despite development of targeted biologicals.

Oxford researchers have identified expression of a particular protein that will be used to stratify metastatic colorectal cancer patients based on their ability to respond to Irinotecan therapy. They have found that the level of expression of a particular protein in cancer cells strongly correlates with the clinical resistance or sensitivity of the cancer cells to particular chemotherapeutic agent.

Primary colorectal carcinoma patients with low or limited expression levels of this protein would be given Irinotecan therapy. However, the patients with high and broad expression of the same protein will not be given Irinotecan therapy and these patients could start straight away with another chemotherapeutic (e.g. oxaliplatin). This approach could save several months of non-effective treatment with Irinotecan.

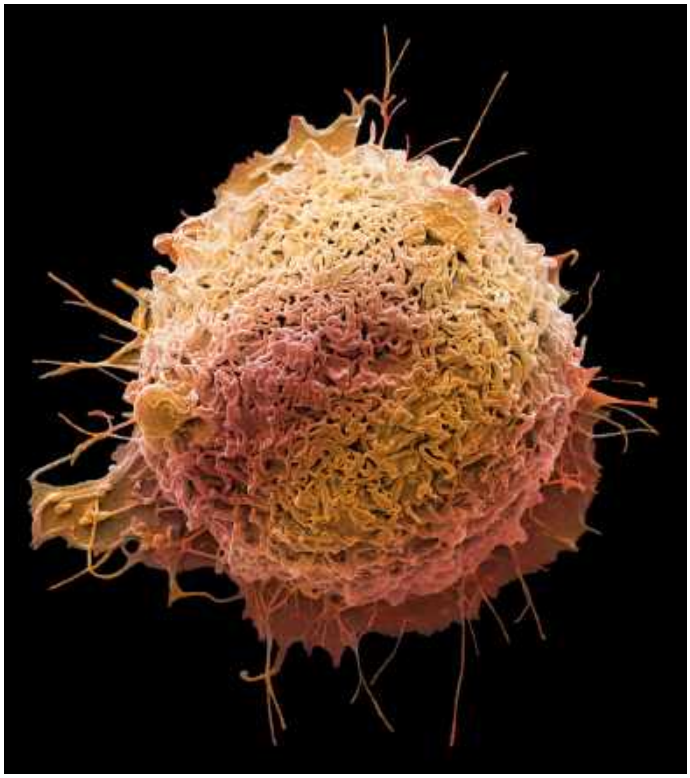

Image: Coloured scanning of a colorectal cancer cell.

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: 16598

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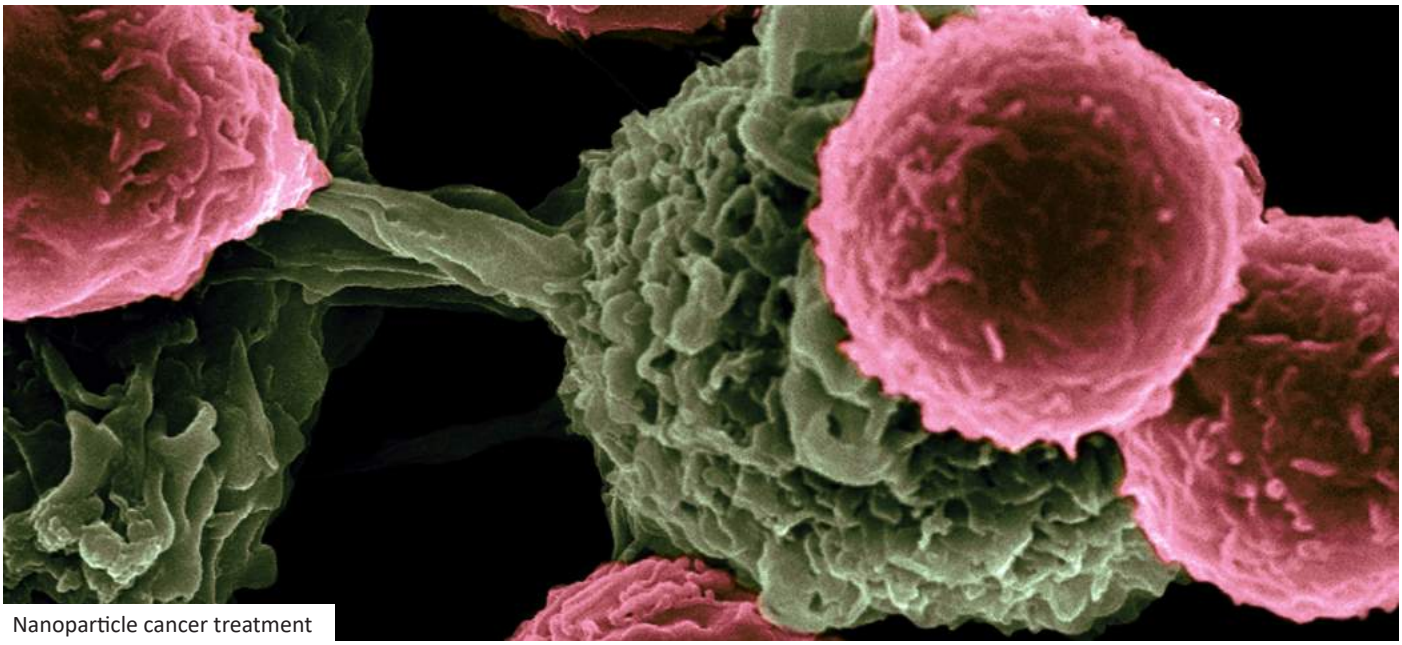
Remote activation and delivery of tissue-specific chemotherapy drugs

Nanoparticle bound thermo-responsive polymers enabling a temporal and spatial controlled delivery of chemotherapy drugs for effective cancer treatment.



Nanoparticle cancer treatment

The use of nanoparticles in cancer treatment

Cancer is one of the leading causes of death in the world that affects all sections of the population and represents a significant economic burden on societies. Chemotherapy is one of the most common cancer treatments and consists of the administration of drugs to destroy cancerous cells. Despite the many lives chemotherapy treatments have saved, the lack of specificity in targeting the cancerous tissue remains a challenge together with the many adverse side effects encountered by the patients such as hair loss, fatigue and breakdown of the immune system among others.

Nanomedicine, on the other hand, has increased in popularity for the treatment of cancer over the past years. Nanoparticles are known to be ideal carriers of drugs and have been shown to accumulate in higher proportions in cancer cells than in healthy tissues.

In addition, nanoparticle carriers can also improve the half-life of drugs meaning that smaller doses are required. Iron oxide and other magnetic nanoparticles are of particular interest due to their ability to be guided to specific locations in the body using a magnetic field. However, until now, scientists have been unable to combine iron oxide nanoparticles with a reliable method to carry and release drugs at the target site.

Radiowave activation of chemotherapy

Researchers at the University of Oxford have successfully combined thermo-responsive polymers with iron oxide nanoparticles to provide targeted delivery and admission of chemotherapy drugs. This technology provides a range of advantages:

- The polymer-nanoparticle complex is capable of retaining a drug while being directed to the target site.
- The drugs are released upon remote heating at a temperature that is harmless to the patient.
- Specific drug combinations can be administered and delivered separately.

This technology would not only improve current chemotherapy treatments, but could also be used to administer a wide range of preventative and therapeutic treatments for a multitude of tissue-specific diseases.

Patent protection

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

For further information please contact:

enquiries@innovation.ox.ac.uk
+44 (0)1865 280830
www.innovation.ox.ac.uk
Project number: 17319

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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

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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:
Amelia Griffiths
amelia.griffiths@innovation.ox.ac.uk
+44 (0)1865 280842
www.innovation.ox.ac.uk
Project number: 11194

Technology Transfer from the University of Oxford

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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

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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.

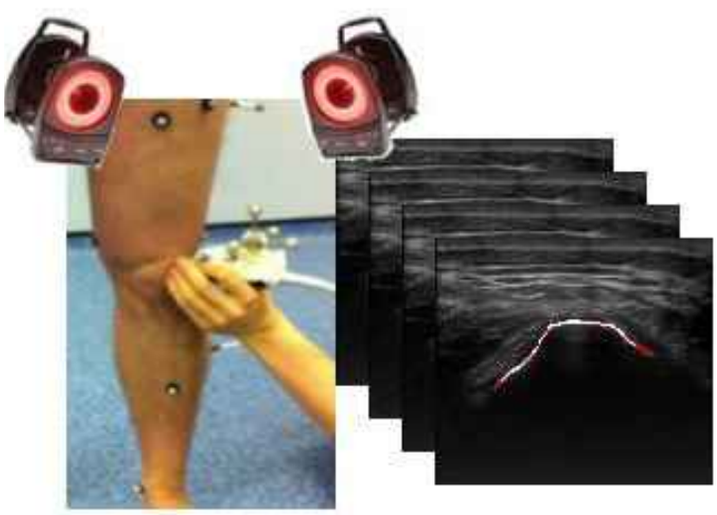
Joint tracker

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

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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

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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:
Dr 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

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Non-surgical distraction orthosis to treat hand arthritis and fractures

A non-surgical removable distraction orthosis for the treatment of hand arthritis and fractures.

Osteoarthritis of the hands and wrist

Osteoarthritis causes the breakdown of joint cartilage and bone. Joint distraction (separation of the joint) mechanically “off-loads” the affected joint. This returns the joint towards its normal biomechanical state, which reduces the forces experienced by the joint tissues.

This allows for regeneration of the joint tissues and relief of the patient’s symptoms.

Treating hand arthritis and fractures

Researchers at the University of Oxford have developed a non-surgical distraction orthosis that has a moulded component that sits at the base of the digit. Distraction arms, one for each side of the digit, extend from the base via a hinge.

The distraction arms are secured to the fingertip, using the nail plate as an anchor. This allows adjustment of distraction on each side of the digit as well as movement at the finger joint. A sensor is being developed to allow feedback on the force of distraction applied.

The benefits of distraction orthosis over other treatments are as follows:

- Disease-modifying treatment rather than symptomatic relief alone
- Avoidance of surgery and the associated harms
- Patient managed treatment
- Design allows the continued use of the hand
- Reduced healthcare costs

In addition to treating osteoarthritis, mechanical offloading of joints and bones can be used to treat joint injuries and fractures through the principle ligamentotaxis.

For further information please contact:

enquiries@innovation.ox.ac.uk
+44 (0)1865 280830
www.innovation.ox.ac.uk
Project number: 15647

Technology Transfer from the University of Oxford

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PRODUCTION/ MANUFACTURING

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

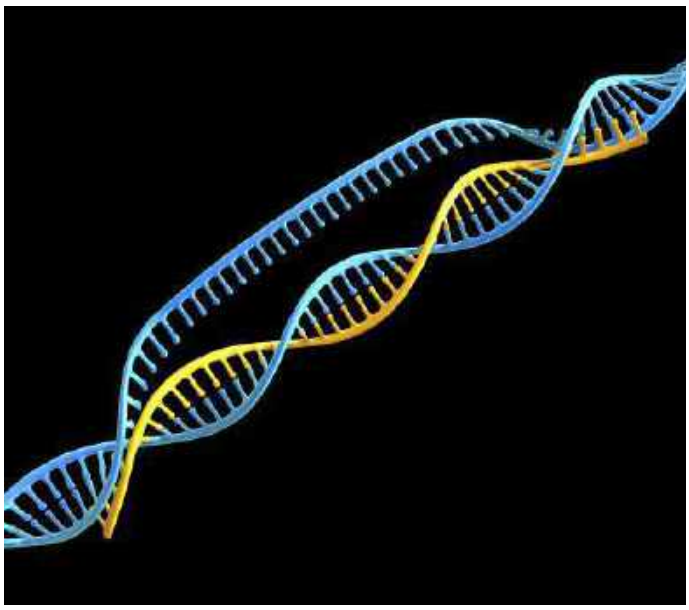
Researchers at the University of Oxford have exploited the triazole linkage in combination with locked nucleic acids (LNAs) to yield oligonucleotides which display higher target binding affinities and greater resistance to enzymatic degradation. In addition, reagents have been developed which allow for 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:
Susan Campbell
susan.campbell@innovation.ox.ac.uk
+44 (0)1865 6 14481
www.innovation.ox.ac.uk
Project number: 14808, 14955

Technology Transfer from the University of Oxford

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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

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New method for the characterisation of amorphous complex mixtures

Oxford researchers have developed an algorithm for the identification of individual chemical components in an amorphous formulation.

Amorphous components in complex formulations

The analysis of mixtures is of particular interest in the development of pharmaceuticals due to regulations and quality control requirements. Although there are a number of techniques currently available for this purpose, the characterisation of amorphous components in complex formulations remains a challenge.

Amorphous solid dispersions (ASDs) comprise an amorphous active pharmaceutical ingredient (API) dispersed in a water-soluble polymer binder. They are commonly used to improve the solubility and bioavailability of the API, making them key in the development of pharmaceuticals. Due to the amorphous nature of ASDs, their stability is poorly understood with re-crystallisation of the API being the most likely cause of a formulation decomposing. In reality, ASDs often contain the API in both amorphous and crystalline form. As the amorphous API is essential to the function of the drug, methods for its characterisation and quantification within the complex formulation are essential. ASDs are currently studied through mass spectroscopy, nuclear magnetic resonance and infrared spectroscopy; however, such techniques struggle to quantify ASDs for formulation purposes and are limited in determining the crystallinity of the API in the ASD.

Novel algorithm for scattering data analysis: characterisation of APIs

Academics at Oxford have tackled such limitation and developed a general and robust method for the characterisation of APIs in complex formulations. The technology relies on diffraction experiments performed on complex mixtures and uses an algorithm to extract the resulting scattering data from each component's contribution.

The new method allows:

- the structural characterisation of an amorphous API in the mixture
- the quantification and monitoring of the crystallinity, which makes possible:

- the determination of the maximum API loading level capable of inhibiting crystallisation

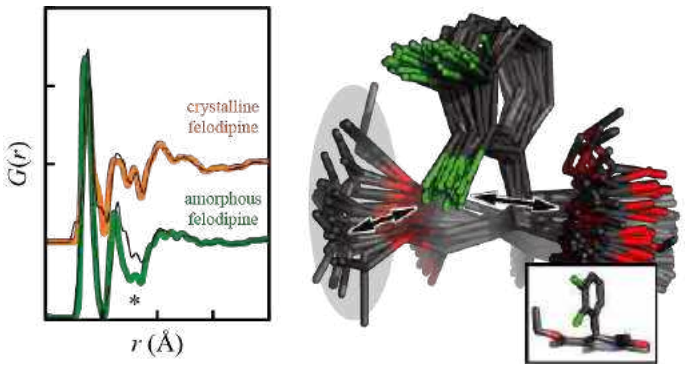
- the identification of drug design strategies for improving stability of the amorphous form

Advantages of the algorithm includes:

- ease of use
- versatility as it can be applied to other experimental datasets including spectroscopy data
- computationally inexpensive
- This same methodology is readily transferable to the study of other complex mixtures beyond those mentioned, such as battery materials, heterogeneous catalysts, and liquid fuels.

Commercialisation

Oxford University Innovation Ltd. has filed an international patent application (PCT) on the technology (WO 2019/180430A1) and welcomes discussions with companies interested in licensing it for commercial development.



Above image: The method enables experimental signatures of both the crystalline and amorphous form of the API to be determined; which allows structural characterisation of the amorphous API in ASDs.

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: 15349

Technology Transfer from the University of Oxford

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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.

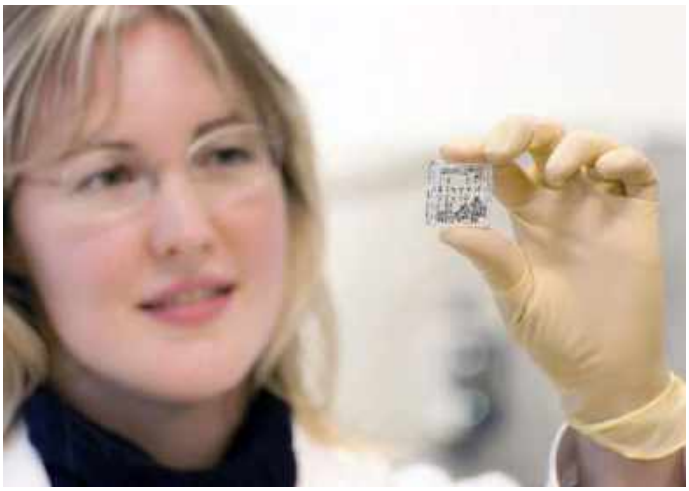
Advantages of this novel technology include:

- 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 Chandra Ramanujan
chandra.ramanujan@innovation.ox.ac.uk
+44 (0)1865 614434
www.innovation.ox.ac.uk
Project number: 16771

Technology Transfer from the University of Oxford

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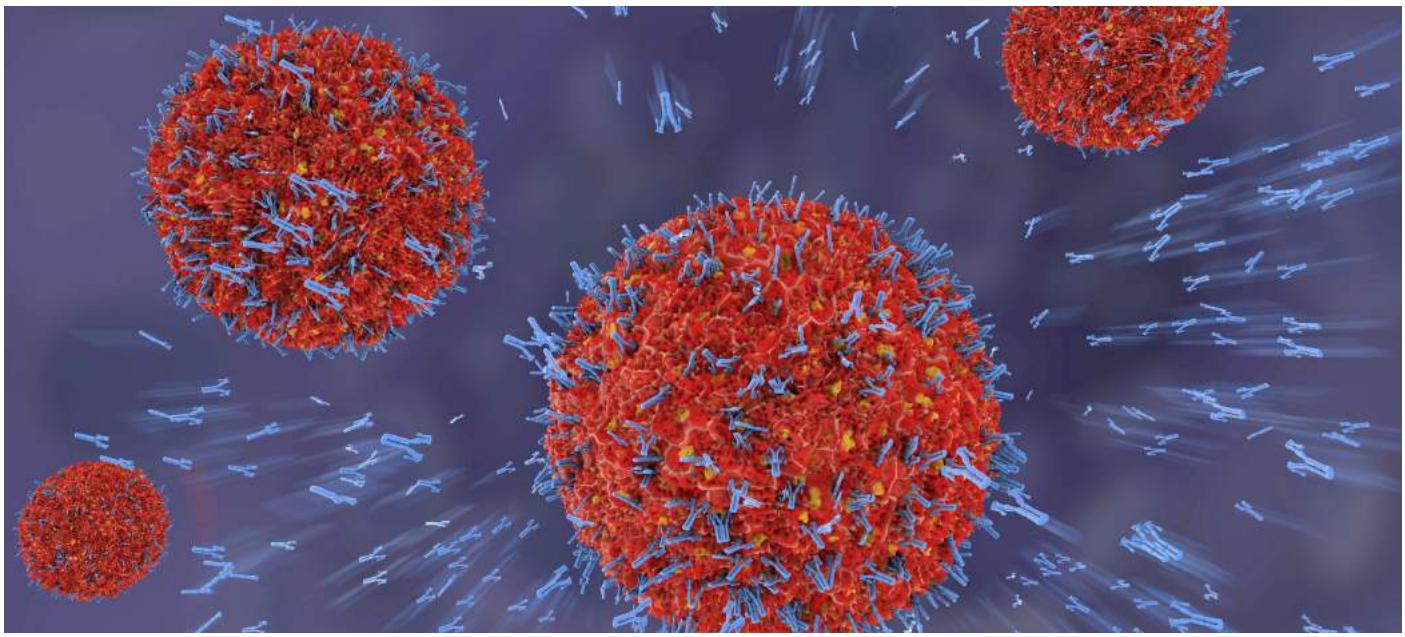
Stabilised viral fusion proteins

Oxford researchers have developed stabilised viral fusion proteins for improved vaccines and protective antibodies against human and veterinary pathogens.



Viral fusion proteins

Viral fusion proteins are classified into Classes I, II or III. Stabilisation of several Class I proteins in the pre-fusion conformation has been reported. However, due to structural differences between Class I and Class III fusion proteins, methods for stabilising Class I proteins cannot be extrapolated to Class III proteins.

To date, only one pre-fusion structure of a Class III fusion protein has been described, and there are no published reports of the successful design of stabilised pre-fusion configurations of any Class III fusion protein in a format suitable for vaccination.

Clinical significance of Class III fusion proteins

Class III fusion proteins are expressed on clinically significant viruses and represent important vaccine immunogens. Class III fusion proteins of the herpesvirus family and the rabies virus glycoprotein (RVG) are the targets of neutralising antibodies with a protective effect. However, some of these antibodies are known to bind only under neutral pH conditions (when protein is in the pre-fusion conformation) and lose binding under acidic pH (when protein adapts post-fusion conformation).

Therefore, there is a need for stabilised forms of the pre-fusion conformation of Class III fusion proteins which can be recombinantly expressed, displaying pre-fusion conformation epitopes capable of stimulating a neutralising antibody response.

Oxford technology

Researchers at Oxford University have identified a region, common to all Class III fusion proteins, that when mutated prevents Class III proteins from transitioning from the pre-fusion to post-fusion conformation. The stabilised pre-fusion conformation Class III fusion proteins retain and display pre-fusion conformation specific epitopes found on the corresponding wildtype protein, and have been recombinantly expressed successfully. By stabilising the pre-fusion conformation, the invention allows enhanced yields of proteins bearing pre-fusion conformation specific epitopes which elicit the production of neutralising antibodies *in-vivo*. This enhanced yield, together with long term stability and antigen quality is advantageous for vaccine production.

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: 17477

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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

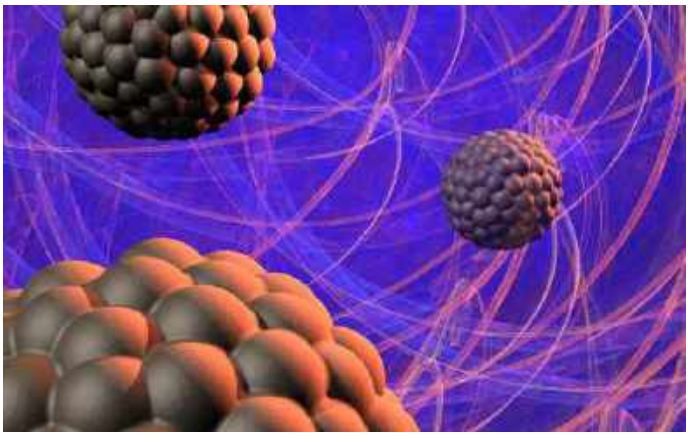
The use of sticky electrodes enables a long sampling time and thus detection of NPs even from media with low concentrations of NPs. The sample can be collected on site without an applied electric potential, i.e. under open circuit conditions. As a result, there is no need to base expensive and sensitive 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

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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.

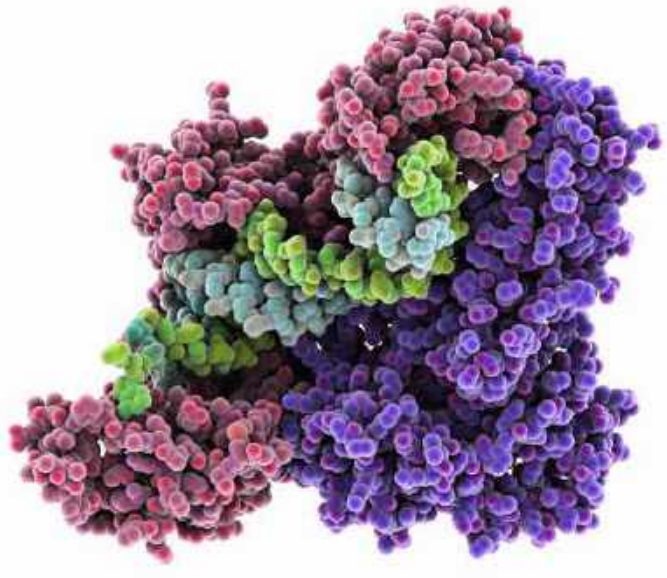
IMPACT (Ion Mobility Projection Approximation Calculation Tool)

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

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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.

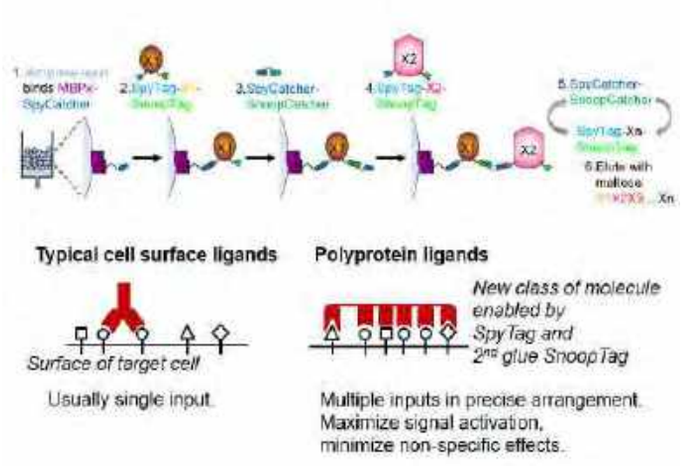
The key properties of SnoopTag/SnoopCatcher-based solid-phase assembly are:

- 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

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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.

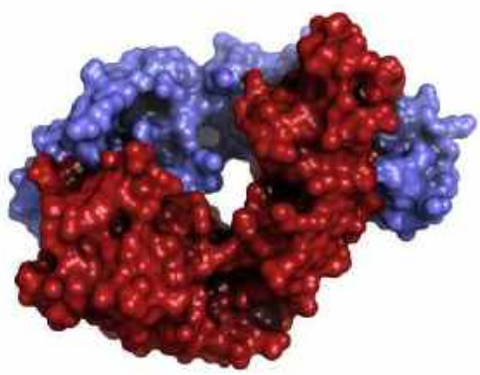
An automated assignment

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

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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).

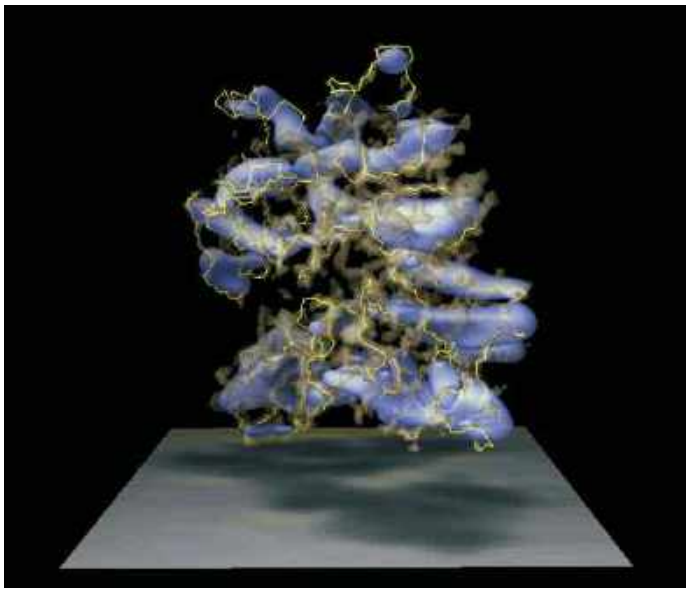
Another piece of Oxford software (IMPACT) is then used to calculate a collisional cross section from the model. This methodology produces a number of possible CCSs, but it is accurately determined by correlation to protein mass.

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

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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

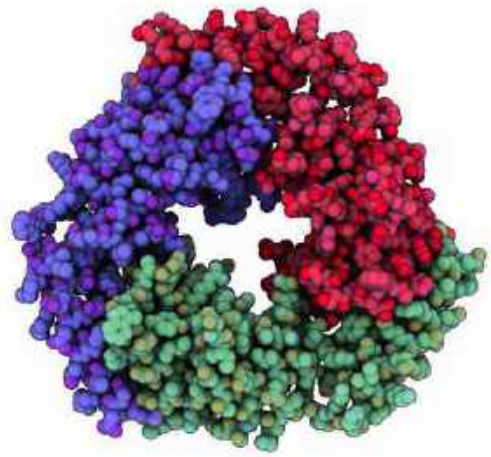
BiobOx allows the user to manipulate and analyse key quantities at all levels of macromolecular structure (primary to tertiary structure). BiobOx can exploit these structures as sub-units to propose highly complex quaternary structures. Structures generated in BiobOx can also be verified using experimentally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

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Multipurpose magnetic microparticles

A method to break the symmetry of the particles by creating ellipsoids (rather than spheres) to produce greater precision, and control at lower magnetic fields.

Magnetic microparticles are used to manipulate small volumes of fluid or other material in a variety of ways and for a large range of purposes. Applications include protein purification, cellular labelling, manipulation of fluids (including detoxification of biological fluids), cancer therapies and magnetofection. Magnetic microparticles are also used to isolate DNA, RNA and viruses and in technological application such as magnetic tweezers and magnetic cell cytometry.

Conventional magnetic microparticles display a spherical shape with magnetic nanoparticles embedded in a polymer matrix. The spherical shape means that it is difficult to create a meaningful magnetic dipole unless large magnetic fields are used. Conventional microparticles have non-homogeneous magnetic properties which are difficult to control, particularly in applications where controlled movement or rotation are required.

The Technology

Micron-sized polymeric particles can be made magnetic by the inclusion of magnetic nanostructures. University of Oxford researchers have developed a method to produce magnetic ellipsoids (rather than conventionally used spheres). The asymmetry of the ellipsoids allows easier control of the movement of the particles by external magnetic fields. The magnetic microparticles are therefore easier to manipulate and lead to more consistent magnetic behaviour throughout a tissue or a fluid. The magnetic microparticles are both biocompatible and biodegradable, raising the potential for use in biomedical applications.

Uses of Superparamagnetic nanowires in Magnetic Microparticles

Magnetic microparticles can be used to manipulate fluids or biomolecules and cells, for a variety of functions. Magnetic microparticles can easily be removed from a suspension after their use, preventing interference which may be seen with other similar methods. The nature of these microparticles means that there are many possible uses for this technology. Identified uses include:

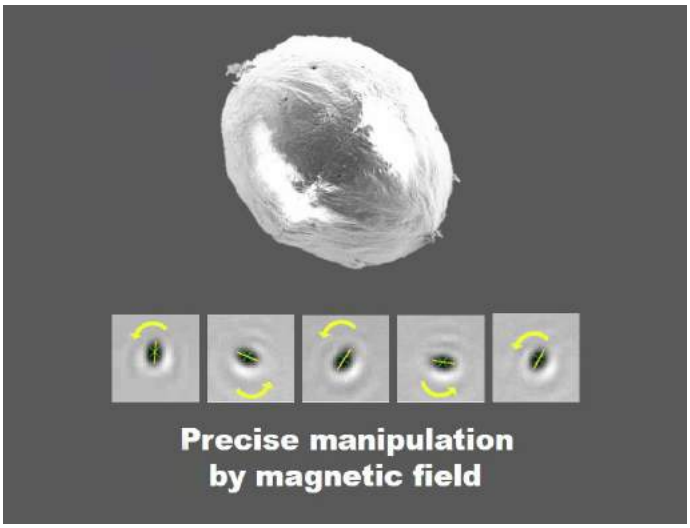
- Magnetic tweezers for biological samples
- Magnetic flow cytometry
- Magnetic mixing of fluids
- Antibody labelling for use in biological assays such as magnetic flow cytometry, ELISAs and cell labelling
- Protein, antibody, DNA, RNA and virus purification and manipulation
- Modular tissue engineering and drug delivery

Advantages of the Oxford magnetic microparticles

- Biocompatible and biodegradable
- Inducible rotation
- Accurate control of movement and travel
- Inducible magnetism - therefore can be switched on and off
- Easily removable from a solution
- A broad range of uses

Commercialisation

This technology is subject to a patent application pending in Europe and the US. OUI is looking to talk to potential partners interested in research collaboration and licensure of this versatile tool.



For further information please contact:

enquiries@innovation.ox.ac.uk
+44 (0)1865 280830
www.innovation.ox.ac.uk
Project number: 13871

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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.

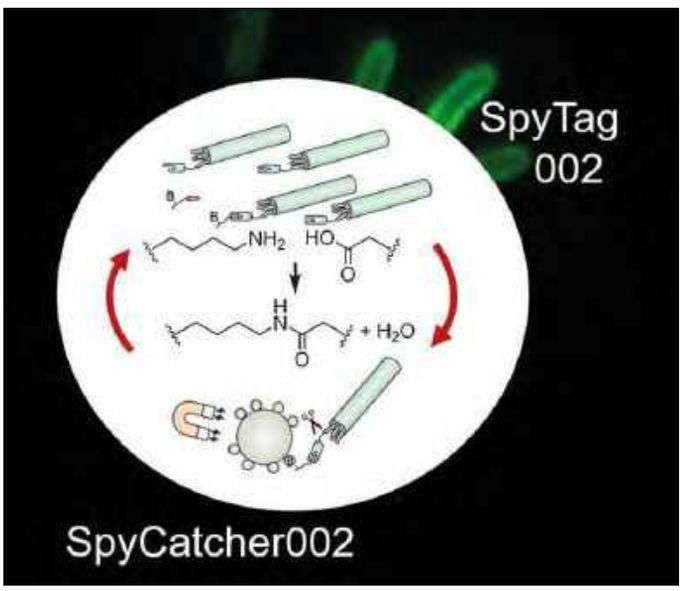
Uses of the technology

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

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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

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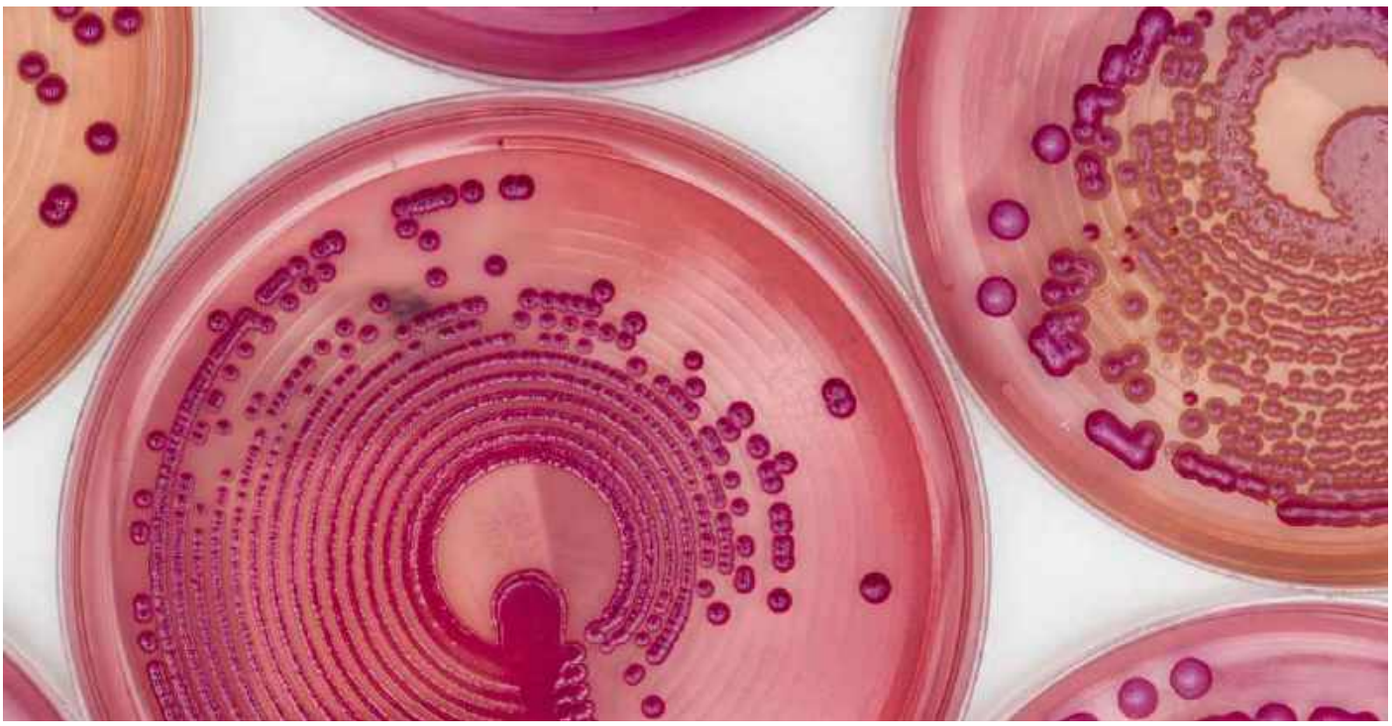
Electrochemical oxidase test for identifying and quantifying bacteria

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 Andrew Bowen
andrew.bowen@innovation.ox.ac.uk
+44 (0)1865 61449
www.innovation.ox.ac.uk
Project number: 15033

Technology Transfer from the University of Oxford

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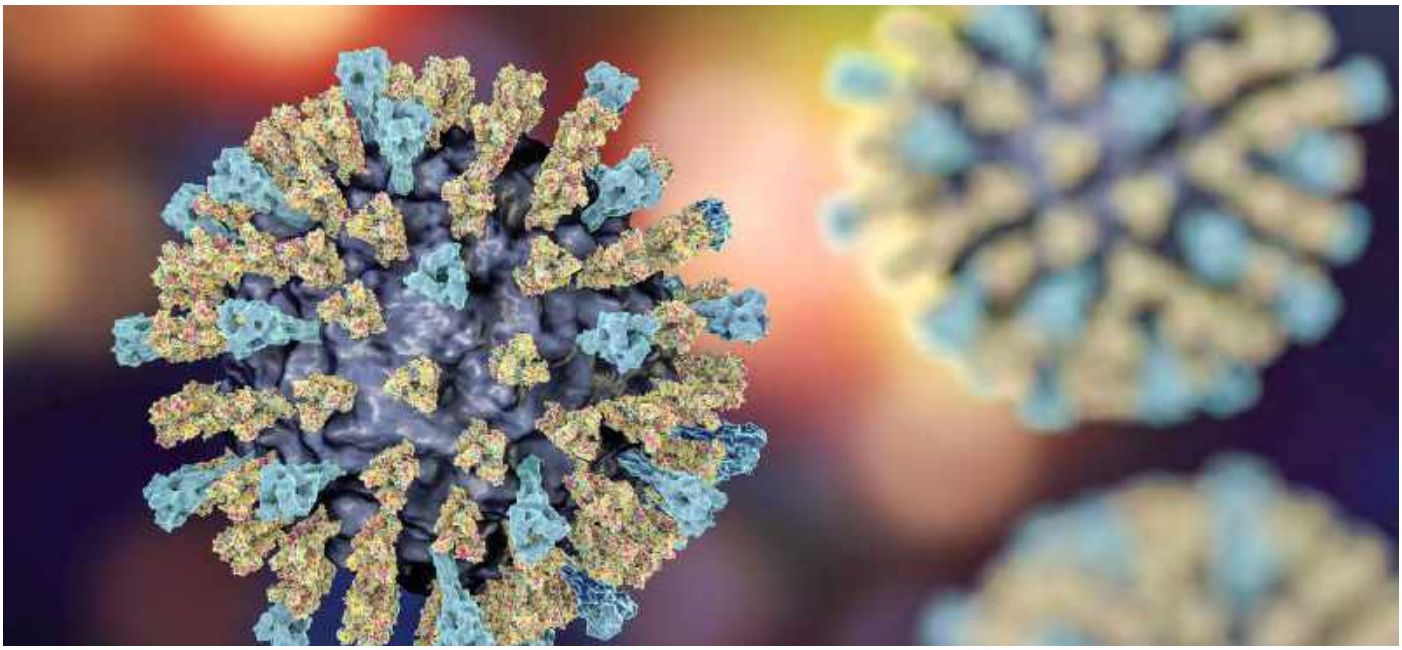
Rapid detection of developed viruses and lipid-coated nanoparticles

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:

ŜyljdzλNλŜă@innovation.ox.ac.uk
+44 (0)1865 нулуол
www.innovation.ox.ac.uk
Project number: 15681

Technology Transfer from the University of Oxford

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INDIANA - IN-cell DIffusion ANAlysis

Researchers at the University of Oxford have developed INDIANA (IN-cell DIffusion ANAlysis), an experimental protocol and software package that offer a quick, accurate and general method for the characterisation of properties in a cell suspension.

Magnetic resonance diffusion experiments

Magnetic resonance experiments provide a non-invasive and powerful method to analyse molecules within cells and tissues. Diffusion methods are frequently used in MRI measurements to provide medical diagnoses, protein folding characterisation and localisation of biomolecules in cellular mixtures.

There has been a number of significant advances in the field of diffusion methods for biological systems; nevertheless, the analysis of data in those systems is challenging due to the inherent heterogeneity inside cells and living tissues. A series of tailored models have addressed those challenges in both homogeneous and heterogeneous samples; however, a general method for cellular systems still seems to be required.

IN-cell DIffusion ANAlysis

Researchers at Oxford have tackled this limitation with the development of INDIANA (IN-cell DIffusion ANAlysis), an experimental protocol and software package that offers a quick, accurate and general method for the characterisation of the following parameters in a cell suspension:

- Cell density and size
- Permeability
- Intrinsic relaxation rates
- Diffusion coefficients

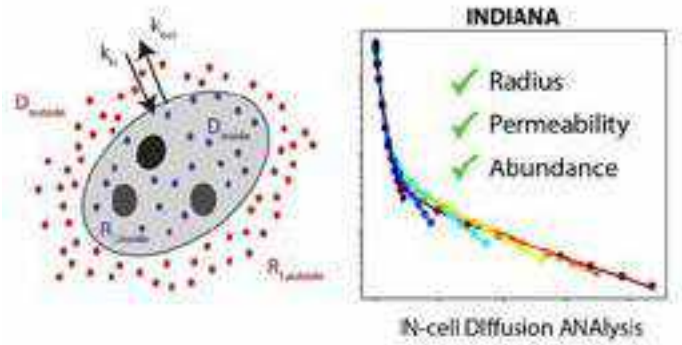
The region of practical validity and the accuracy of the fitted parameters were determined and,optimised for the study of eukaryotic cells by NMR. Experimental endorsement of the model also proved the utility of the technology.

Applicability of the method includes:

- Analysis of any molecule that can be spectroscopically resolved – the isotopic enrichment would allow for background-free measurements
- Monitoring of cell preservation in perfusion systems
- Diffusion MRI

Commercialisation

Oxford University Innovation is currently seeking academic and commercial users for INDIANA. Please see our online software store for more information https://process.innovation.ox.ac.uk/software/p/16405/indiana-(academic-use-only)/



IN-cell Diffusion ANAlysis

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: 16405

Technology Transfer from the University of Oxford

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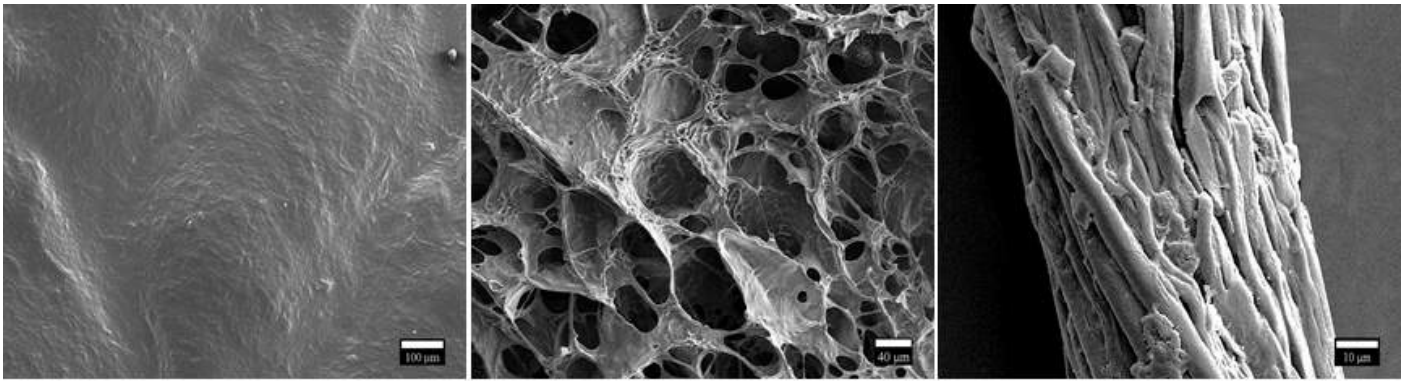
A new form of natural elastin with gel-like properties

Oxford researchers have developed a method to modify natural elastin into an insoluble gel with improved elasticity, resilience and bioactivity for biomedical applications.



Dense films | Porous foams | Self-assembled fibres

The use of elastin in biomaterials

Elastin is a key protein of the extracellular matrix, known for its role in providing elasticity and resilience to compliant connective tissues. Elastin can be exploited in various forms, including synthetic peptide sequences or tropoelastin. However, these soluble forms are limited by the requirement of extensive cross-linking, often, at the expense of their biocompatibility. In comparison, naturally derived insoluble elastin can be extracted and purified from tissues to produce insoluble elastin fibres.

Natural forms of elastin have been limited as biomaterials to date due to their inherent insolubility (polymeric elastin) or loss of structural integrity due to complete hydrolysis (α-elastin).

A new form of natural elastin

The methodology developed by researchers at the University of Oxford modifies natural insoluble elastin to an insoluble elastin gel which has improved reactivity with solvents and therefore can be processed into multiple structures. The unique material provides several advantages over current forms of natural elastin:

- The manufacturing of 3D structures of all shapes and sizes, including dense films and highly porous foams.
- The gel exhibits self-assembly properties which could be used to fabricate bioinspired constructs using the “bottom up” approach. It has also been shown to be pH- and thermo-responsive which could be exploited for applications in therapeutic delivery.
- The gel is biocompatible and biodegradable and can be combined with other structural materials to form functional composites which maintain flexibility, resilience and low hysteresis.
- The gel is bioactive and has been shown to upregulate elastin expression. This is important as the expression of elastin is downregulated in adults and current biomaterials promote the synthesis of suboptimal levels of elastin by cells.

The team have successfully produced bioactive and biocompatible scaffolds with this new form of elastin and are now looking into testing new scaffold structures in animals.

Licensing opportunity

Oxford University Innovation is seeking a commercial partner to further develop and bring to market this new biomaterial under an appropriate collaboration.

For further information please contact:
Iraida Soria Espinosa
iraida.soriaespinosa@innovation.ox.ac.uk
+44 (0)1865 614453
www.innovation.ox.ac.uk
Project number: 16826

The information in this Project Profile is provided "as is" without conditions or warranties and Oxford University Innovation makes no representation and gives no warranty that it is the owner of the intellectual property rights in the technology described.

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Multi-functional air flow thawing apparatus

Oxford researchers have developed a novel reagent rack specifically designed for thawing large numbers of samples at a time either through a heated or room temperature air flow.

Scientists at the University of Oxford have created a reagent rack that has been designed to allow a machine-generated air stream to flow through to accelerate thawing of samples. Not only is the thawing device inexpensive to produce, it can considerably accelerate the thawing of samples or reagents for laboratory use.

It is designed specifically to thaw large numbers of samples or reagents at a time, either through a heated or room temperature air flow. The device creates an air flow that thaws the content of samples placed in the rack, which can also be heated. When a sample tube thaws at room temperature, a layer of still, cool air is soon created around it thus slowing down thawing speed. By creating an air flow, this layer of cool air does not form and the samples thaw more quickly.

Furthermore, heating the air flow can further accelerate the speed of thawing. By including a number of inexpensive elaborations, the researchers also successfully used the same apparatus to perform restriction enzyme digestions, cell growth and polymerase chain reactions.

To prepare a substance for a reaction, it may be necessary to alter the physical state of the substance. For example, should a reactant be frozen (e.g. for storage purposes), the reactant may need to be thawed before the reaction can begin or for the reactant to be mixed with other reactants. It may also be necessary to bring reactants to a specific temperature to start the reaction or to bring a reactant mixture to a specific temperature to trigger a specific step in a multistep reaction.

Certain reactions may also require to be held at a constant temperature for an extended, set period of time. A number of techniques and apparatus are capable of performing these processes.

However, often a technique or apparatus which is appropriate for performing one of these processes may not suitable for performing another.

Thawing of frozen reactants is often performed using the heat generated by an individual's hands. An individual may rub a vial containing a reactant between their hands to thaw the reactant. Not only is this a time-consuming, labour intensive thawing process for the individual, it is also highly inefficient as only one vial of reactant can be thawed at a time. Such a technique may also be unsuitable for reactions which require a precise, constant temperature and/or a series of temperature changes.

In some cases, a substance may be kept at a constant temperature for an extended or set period of time by a heat block. In other cases, a thermal cycler may be used expose a reaction mixture to a multiple temperature sequence. However, both of these items are complicated and bulky which may make them unsuitable for smaller laboratories or laboratories with more limited resources.

This invention provides an inexpensive reagent thawing apparatus which overcomes the limitations of current technologies by providing an improved and more efficient method of controlling the temperature of substances for a range of common laboratory reactions.

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: 16887

Technology Transfer from the University of Oxford

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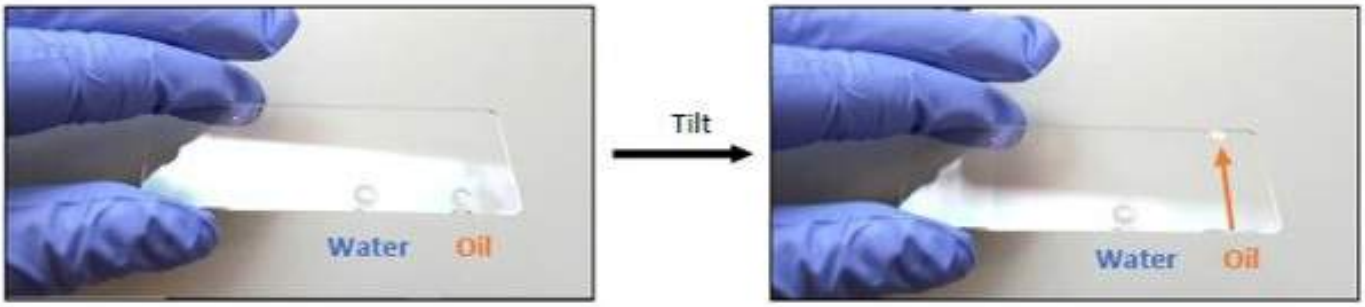
A polymer coating that is selectively sticky for water but not oil

University of Oxford researchers have developed a transparent polymer coating that could potentially be used for oil/water separation.



The global oil-water separation market is projected to reach 9.13 billion USD by 2022. The separation of oil and water is an integral step to protect the environment from oil-containing wastewater that is produced in many industries.

Researchers at the University of Oxford have developed a polymer coating that causes unusual, yet desirable, wetting characteristics. The polymer's characteristics result in a surface that is selectively sticky for water and not oil.

The coating is sticky yet repulsive to water meaning that a water droplet will remain adhered to the surface, even when tilted 90°. On the other hand, the coating is slippery yet attractive for oils meaning that an oil droplet will slide off a tilted surface and leave no residue.

These hydrophobic and oleophilic properties are created during a one-step procedure for synthesis of a transparent smooth surface coating. The copolymer is simultaneously synthesised and coated on to a substrate via low-pressure pulsed plasma polymerization. This process creates a transparent coating that can separate oil from water.

Furthermore, this polymer coating could also be used for self-cleaning, anti-fouling and anti-fogging purposes.

For further information please contact:

enquiries@innovation.ox.ac.uk
+44 (0)1865 280830
www.innovation.ox.ac.uk
Project number: 17035

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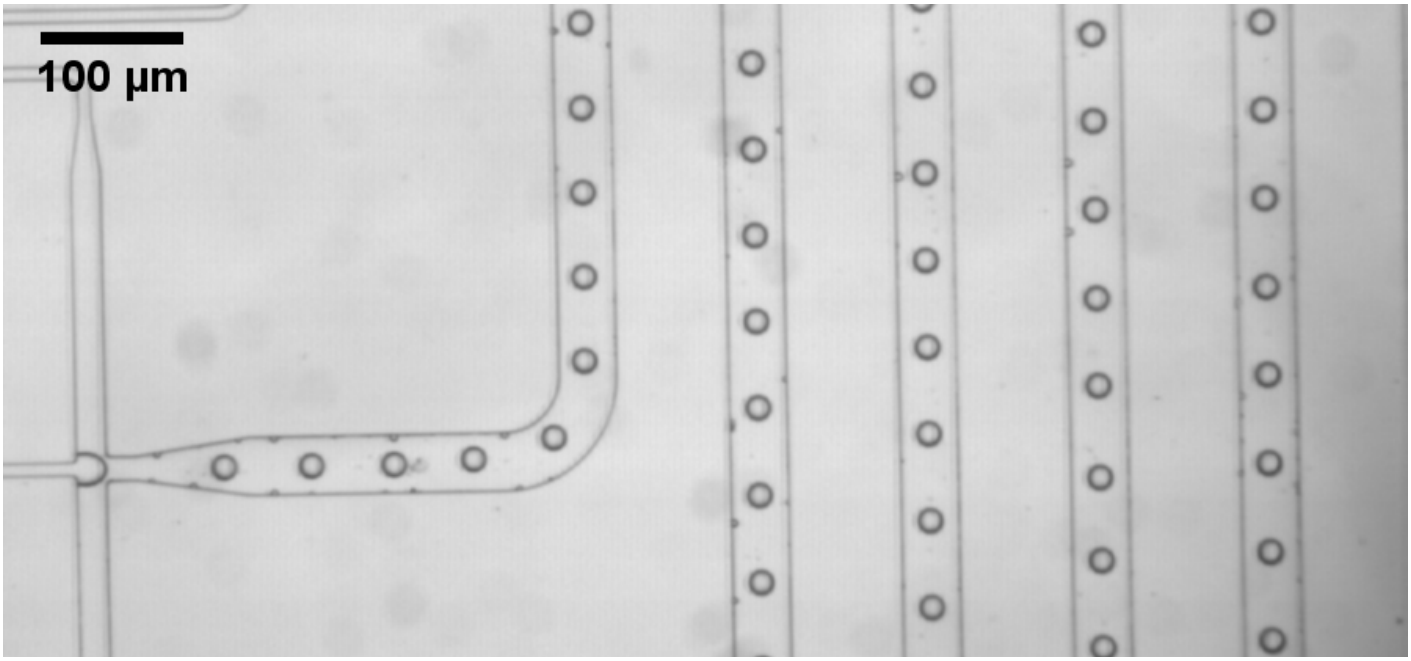
Rapid high precision microencapsulation for controlled release

Oxford researchers have developed a microfluidic hydrogel pre-encapsulation method of making coated hydrogel beads.

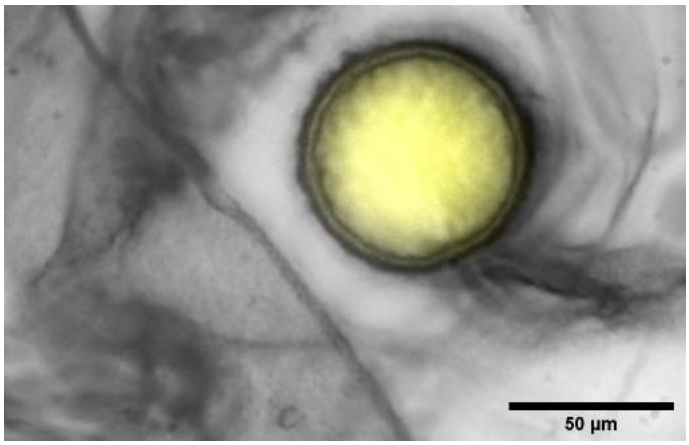


Scientists at the University of Oxford have developed a technique that can be used in the pharmaceutical and food industries to encapsulate a wide range of molecules for controlled delivery. The method ensures the production of a complex multi-layered system avoiding the limitations of both conventional manufacturing methods and standard microfluidic approaches. The method is characterised using a high degree of control over production parameters and physical-chemical characteristics of the produced particles, while offering flexibility to tailor to the specific release kinetics needed. The technology can be particularly advantageous in industry to enable the production of more complex drug delayed delivery systems.

Current methods to encapsulate substances such as drugs and cosmetics include the formation of double emulsions. A double emulsion, droplets of a dispersed phase, contain one or more types of smaller dispersed droplets within themselves. This technique has many drawbacks, including the formation of microparticles with a broad size variation, inconsistent loading, and prolonged exposure to organic solvents.

Furthermore, the existing techniques lack precise control over physical characteristics (e.g. core size, particle size thickness etc.) all of which are important for controlled release systems.

The Oxford team has sought to address the problems by developing a method to produce hydrogel beads with more homogeneous and reproducible size range, excellent encapsulation efficiency and the ability to tailor release kinetics on demand with relative ease. Although this technology is particularly suited to drug delivery, it has application in other industrial encapsulation processes such as food, cosmetics, paint and in vitro cell culture.



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: 17072

Technology Transfer from the University of Oxford

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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

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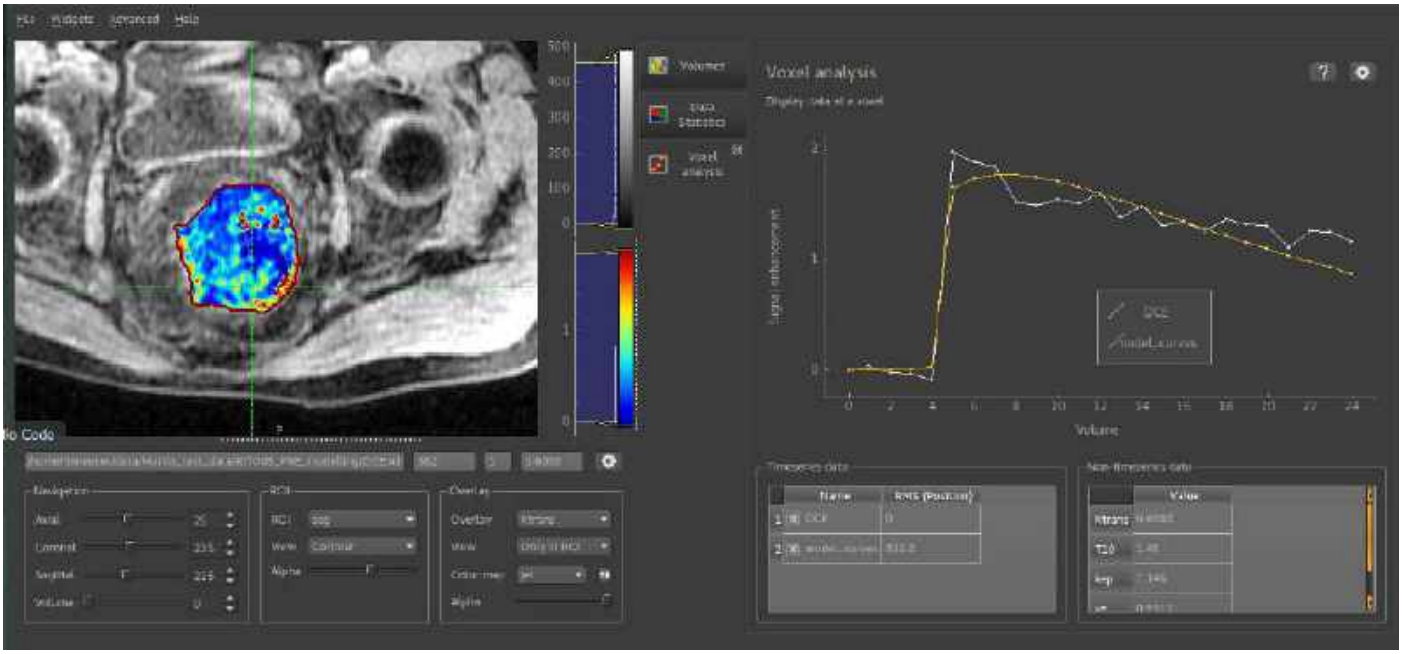
Quantiphyse - Improved analysis of biomedical imaging data

Researchers at the University of Oxford have developed a tool to accurately view and analyse biomedical imaging data.



Over the years, medical imaging techniques have undergone major advances. The most common types of imaging include X-rays, ultrasound, CT scans and MRI.

Quantiphyse is an advanced visual tool for 3D and 4D (time) biomedical imaging data. It is particularly suited for physiological or functional imaging data comprised of multi volumes in a time series and /or multimodal imaging data. Applications of the software tool include highlighting features in the brain and cancerous growths associated with the underlying physiology.

The software is capable of generating spatially resolved measurements of physical or physiological processes from imaging data using either model-based or model-free methods. It relies, in large part, on exploiting Bayesian inference techniques.

Quantiphyse can analyse data both voxelwise or within regions of interest that may be manually or automatically created, e.g. supervoxel or clustering methods.

Key features include:

- 2D orthographic viewing and navigation of data, regions of interest (ROIs) and overlays
- Universal analysis tools including clustering, supervoxel generation and curve comparison
- Tools for CEST-MRI analysis and modelling
- Tools for DCE-MRI analysis and modelling
- Tools for ROI generation
- Registration and motion correction
- Extensible via plugins, in the future to include ASL MRI data, Bayesian modelling and more

Quantiphyse is now available directly through the Oxford University Innovation Software Store.

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: 14419

Technology Transfer from the University of Oxford

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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

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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.

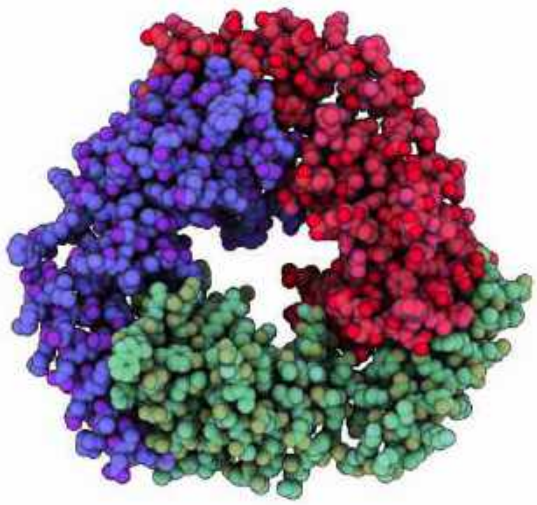
The software also:

- 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

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AFIRM: Amyloid Formation and Inhibition Mechanism

Available to license: Software for the determination of amyloid formation mechanism and how this is inhibited by the addition of drugs, using nuclear magnetic resonance (NMR) spectroscopy.

Oxford researchers have developed an efficient software platform and associated experimental protocols for the determination of a complete molecular amyloid formation mechanism, and how this is perturbed by the addition of small molecules, proteins and molecular chaperones.

Amyloid mechanism

Many disorders including Alzheimer's and Parkinson's diseases are associated with amyloid formation and deposition in tissue. Improved understanding of the molecular mechanism of amyloid formation, and how this is perturbed by small molecules, proteins and chaperones is expected to support the discovery of diagnostic tests and therapeutics for such neurodegenerative diseases. Our method directly addresses this need.

Platform for mechanism determination

Oxford University researchers have developed an approach for mechanism determination. NMR spectroscopy can quantitatively follow the specific changes in aggregating molecules without the need for the addition of, for example, fluorescent tags. This method functions in the context of heterogeneous non-equilibrium mixtures such as inside cells.

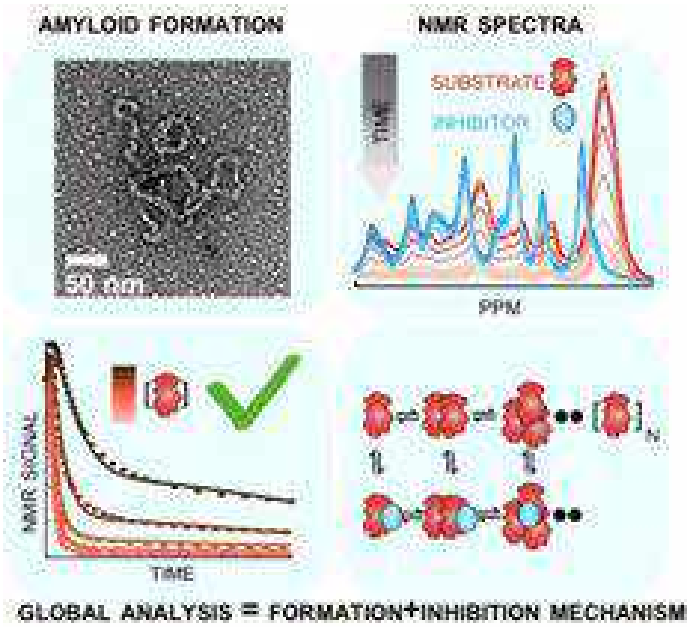
The approach provides experimental protocols for obtaining reproducible kinetic data, and globally analysing it to provide a molecular description of underlying events.

The AFIrM method has the following key features:

- Early events including the formation of primary nuclei can be identified and characterised.
- No normalisation of the data is required – this allows for a complete thermodynamic, as well as a kinetic description of the aggregation mechanism and inhibition mechanism.
- Method works in the presence of complex mixtures and in the presence of living cells.
- Software numerically efficiently evaluates rate equations allowing for exact testing of aggregation mechanisms of arbitrary complexity.

Commercialisation

Oxford University Innovation is interested in speaking to companies that would like to use our facilities as a service or license this software for in-house use.



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: 14905

Technology Transfer from the University of Oxford

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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.

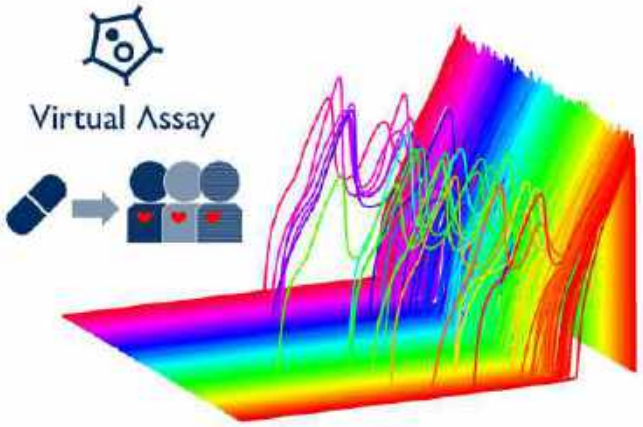
"Virtual" screening with Virtual Assay

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

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An early warning system to predict clinical deterioration

Oxford researchers have developed an attention-based early warning score to identify in-hospital clinical deterioration using routinely collected data in electronic medical records.

Increased access to Electronic Health Records (EHR) has motivated the development of data-driven systems that detect physiological derangement and secure timely response. Commonly predicted adverse events such as mortality, unplanned ICU admission and cardiac arrest, have been extensively investigated by early warning systems (EWS), such as the National Early Warning Score (NEWS) that is currently recommended by the Royal College of Physicians in the UK. Typically, EWS systems assign a real-time alerting score to a set of vital sign measurements based on predicting risk to indicate the patient's degree of illness.

However, physiological data recorded in EHRs are often sparse, noisy and incomplete, especially when collected in non-critical care wards. Missing information is often dealt with through complete-case analysis, population mean imputation, or carrying the most recent value forward. Such practices may impose bias and error and do not account for the uncertainty of the data.

Scientists at the University of Oxford have developed a novel approach to address these issues.

They have developed an end-to-end framework which provides data pre-processing, patient-specific data modelling, and generates early warning scores to prevent adverse events which directly affect patient outcomes when undetected. Unlike the traditionally heuristic early warning scores, this system utilises deep learning with attention for enhanced patient risk stratification and improved model interpretability by clinicians. Each vital sign of each patient is initially modelled using a machine learning approach.

The modelled and regularly sampled vital signs are then classified according to this approach. The invention is useful towards predicting the risk of other adverse events and generally precision medicine, such as wearable health monitoring.

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: 16385

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Curator: Software for the advanced curation of real-world clinical data

Researchers at the University of Oxford have developed a platform for the automatic management, organisation and advanced curation of clinical data to support real-world data studies.

Challenges in big data

Real-world clinical data has become an invaluable source of information used in academia and industry to support evidence-based research, advise health-care delivery, and support new therapy development. Unfortunately, reproducibility, transparency, feasibility, and accuracy are placed at risk when these datasets are not parsed using expert-level tools. The vast amounts of data alone often present challenges to statistical approaches that can become unnecessarily slow, expensive and error prone.

An innovative solution: Curator

Researchers at the University of Oxford have developed a new solution to these challenges with the creation of the innovative data science tool Curator. Curator performs automated data engineering, data mining and advanced curation on electronic health records to provide tailored clinical datasets. Data are efficiently, accurately, and consistently curated and delivered in a format that is ready for statistical analysis.

Thanks to Curator's scalable design, the tool can be applied to a wide range of datasets including those provided by Clinical Practice Research Datalink (CPRD) and NHS Digital. Curator can be expanded as additional clinical datasets become available. To date the software has supported more than 20 observational studies that span a broad spectrum of conditions and therapeutic investigations. Curator consistently saves time, reduces costs and improves both research quality and reproducibility.

The tool confers the following benefits:

- A vast clinical scope including common chronic conditions
- Significantly reduced time and costs per study
- Reduced human error by supporting reproducibility and facilitating comparisons within and between studies
- No direct competitors

Commercialisation

Oxford University Innovation is interested in speaking with companies or institutions that would like to test and adopt this tool to improve their processing and statistical analysis of real-world data.

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: 17185

Technology Transfer from the University of Oxford

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Career Weaver: A web based application to identify core career drivers

The University of Oxford Careers Service has developed an app which provides exercises to identify and articulate work related values, interests, motivation, skills and strengths.

Current career planning tools

Many online career planning resources provide users with a bank of questions and a 'black box mechanism' that presents 'answers'. Career Weaver is designed to enable users to uncover and define for themselves hidden (or part hidden) aspects of their habits, preferences and patterns of work that relate to their successes and life satisfaction.

By bringing together a diverse set of exercises, Career Weaver offers a variety of structured approaches and language, differing from most tools in this field which use a single lens approach.

Oxford technology: Career Weaver

The Careers Service at the University of Oxford has developed a distinctive approach to career planning with this web based application. Career Weaver challenges and guides users to identify their underlying career drivers, facilitating both a richer understanding and clearer articulation of those drivers.

The range of exercises embedded within Career Weaver creates a stimulating and engaging electronic environment.

The variety in the methods of play promotes exploration and embraces differing work styles and preferences so that everyone can uncover, define and capture their most important work-related drivers.

Using Career Weaver

For people in employment, Career Weaver may be used to improve focus and understanding of personal goals and developmental needs.

For students, graduates/alumni and job seekers, Career Weaver can enable a focussed job search, and improve the quality of applications and interview performance throughout the job-hunting process.

Career Weaver is currently provided by the Oxford University Careers Service as a stand-alone tool to support independent reflection and career planning by individuals. It is also fully integrated into the workshops and discussions that are central to the advisory service offered to students, alumni, and University staff. We at Oxford believe that the tool could be of interest to the career services of other HE institutions, as well as private individuals and staff in work settings.

With additional development, the content and style of Career Weaver could be adapted to suit a younger audience such as school children or young people in key stages three or four.

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: 17782

Technology Transfer from the University of Oxford

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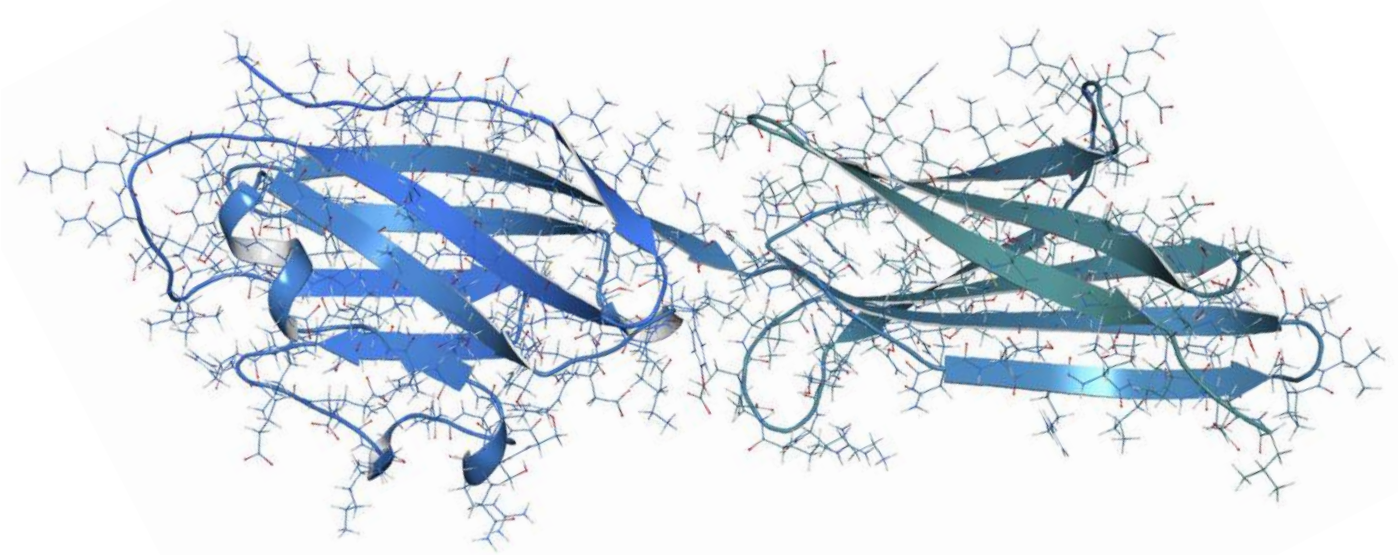
Computational antibody modelling and prediction – SAbPred singularity platform

Oxford researchers have improved the usability of SAbDab-SAbPred tools for structural antibody modelling and prediction into a singularity container for secure use on any Unix-based system.



Antibodies are proteins that form the backbone of the human immune system. These molecules are highly designable allowing them to be harnessed as therapeutics. This makes antibodies the most prominent class of biologics, with a current market value of ~£70b.

At present, antibody therapeutics are developed using experimental pipelines that are very expensive, which in turn pushes up the price of the resulting drug. Facilitating this process by reducing the number of required experiments has the potential to accelerate and reduce the price of drug design.

Recent advances in understanding antibody structure and function have allowed the development of software that facilitates antibody engineering in this manner. Research led by Charlotte Deane, Professor of Structural Bioinformatics, is pioneering the development of such software and its dissemination to the pharmaceutical industry.

The Oxford protein informatics group

Prof Deane's research group have developed the Structural Antibody Database (SAbDab) and Structural Antibody Prediction Platform (SAbPred) for the computational design of antibodies. The former collects and curates structural information on antibodies and the latter uses this data to perform modelling and prediction tasks that support antibody design. The software helps to prioritize which antibodies should be investigated further, and even to design entirely new antibodies.

The platform is currently used by leading biopharmaceutical companies to improve the design of antibody-based therapeutics.

The SAbDab-SAbPred platform is currently available for download and plug and play use as a Singularity container. Singularity uses a lightweight form of virtualisation which allows a Linux distribution with all its software to run in a special environment on top of an existing Unix-based operating system, such as Linux, macOS, or the Windows Subsystem for Linux.

The SAbDab-SAbPred Singularity container provides all the SAbDab-SAbPred tools in a single, portable format. Using the container, it is possible to run any of the SAbDab-SAbPred on any system with a Singularity installation without the need for any additional software installation, and the container can be easily managed and transferred between systems.

Unlike a virtual machine, software in a Singularity container runs at close to bare metal speed, without the performance overheads typically associated with virtualisation, resulting in optimal performance across all compatible systems.

For further information please contact:

enquiries@innovation.ox.ac.uk
+44 (0)1865 280830
www.innovation.ox.ac.uk
Project number: 20120

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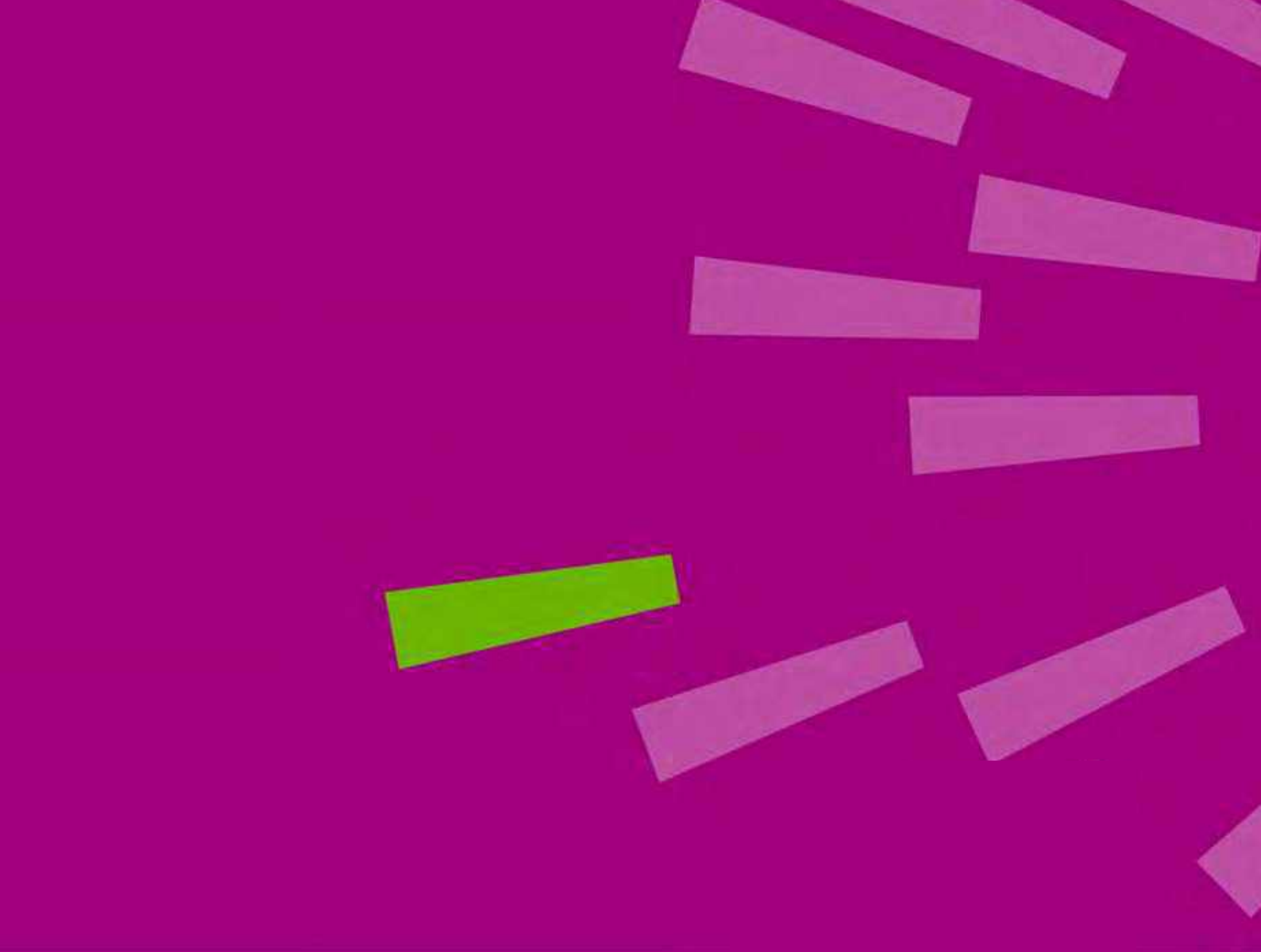


TARGETED THERAPIES

Antibiotic

Non-toxic carbohydrate based inhibitors of the protective capsule formation in pathogenic Gram-negative bacteria, for use as antibacterial agents.

Antibiotic resistance is a serious and growing threat in contemporary medicine, emerging as one of the pre-eminent public health concerns of the 21st century. Some 125,000 people across Europe and the USA die every year due to bacterial infections resistant to antibiotic treatments. Within these regions, drug-resistant bacteria inflict an additional financial burden on healthcare systems through exaggerated medical costs of up to $35 billion. Despite this looming crisis, the pharmaceutical industry has been slow to develop new antibiotics, with the pipeline of future treatments described by the World Health Organisation as “virtually dry”.

Cell wall disruption

Oxford researchers have explored a new approach for treating infections caused by gram-negative bacteria, based on non-toxic carbohydrate drug candidates. A class of inhibitors has been identified that weaken bacteria by specifically damaging their outer cell wall, making them vulnerable to attack by the host’s own immune system.

The lead drug candidates have been shown to act at the outer membrane of bacteria from the extracellular environment without entering the cell. This allows a greater diversity of chemical functionalities of the candidates without necessarily following the general rules for properties of existing antibiotics.

Advantages vs traditional treatments

- Non-toxic to probiotics within the host
- Accessible to targets located on the outer membrane of bacteria (no cell penetration)
- Specific to the transporter of the outermost protective layer of Gram-negative bacteria (novel target)
- Effective as a potentiator of the host’s anti-bacterial immune system

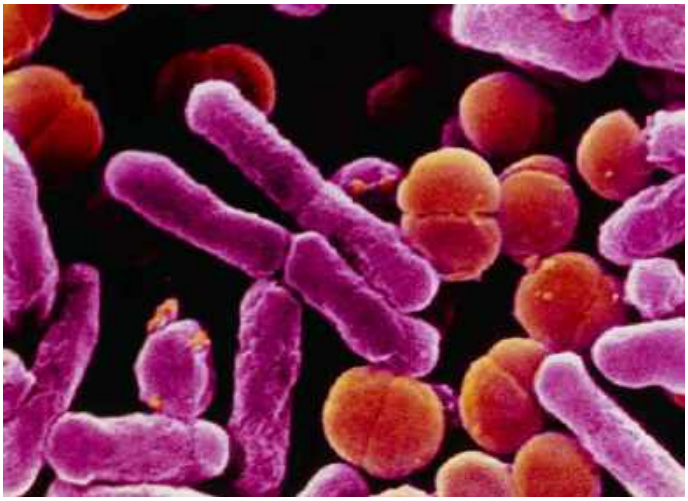
This novel mode of action, general target protein family and greater structural latitude provide clear strategic advantages and dramatically decrease the possibility of acquired resistance. Compounds with similar structures to the Oxford blockers are stable and safe in humans, making the carbohydrate based leads very promising drug candidates.

Additional applications

The Oxford compounds are not only active as anti-bacterial agents in therapeutic treatments. It is also possible for them to be incorporated into cleaning agents, deodorisers, sportswear and wound dressings.

Licensing opportunity

The underlying technology is the subject of a PCT patent application and Oxford University Innovation welcomes contact from parties interested in developing this opportunity.



For further information please contact:
Andrew Bowen
Andrew.Bowen@innovation.ox.ac.uk
+44 (0)1865 614449
www.innovation.ox.ac.uk
Project number: 7876

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Gene therapy for chronic pain and epilepsy

Available to license: An adeno-associated virus based gene therapy delivering CASPR2 as a possible treatment for chronic pain and epilepsy.

Researchers at Oxford have identified a new approach to treat chronic pain and epilepsy based on the overexpression of a modified CASPR2 polypeptide in sensory neurons.

Current treatments for chronic pain and epilepsy do not fully satisfy all clinical needs. In the case of chronic pain, epidemiological data shows that one in five adults is affected despite the use of current analgesics. It has a detrimental impact on an individual's quality of life and results in huge economic costs to society as a whole, much greater than those attributed to heart disease or diabetes. Opioids and NSAIDs are the most commonly prescribed analgesics, but are associated with significant side-effect profiles. Furthermore, these drugs rarely provide adequate pain relief and are particularly ineffective against chronic pain caused by nerve injury (neuropathic pain).

Neuronal hyperexcitability is a key feature underlying neuropathic pain (and epilepsy). CASPR2 (contactin associated protein 2), a member of the neurexin family of proteins, regulates the function of potassium channels. These channels are key determinants of neuronal excitability and loss of their activity is implicated in neuropathic pain and epilepsy. Furthermore, disruption of CASPR2 by autoantibodies is associated with neuropathic pain and epilepsy in patients. Researchers at Oxford have shown for the first time that CASPR2 is directly involved in regulating the excitability of sensory neurons. The overexpression of CASPR2 reduces neuronal excitability and can be used as the basis for a method to treat pain, excessive neuronal activity and epilepsy.

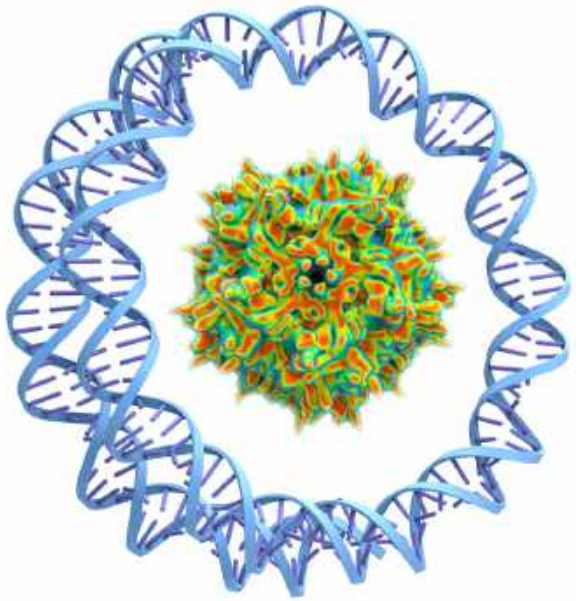
A new approach

Based on these findings, Oxford researchers have developed a potential gene therapy to treat chronic pain and epilepsy. The gene therapy consists of an adeno-associated viral vector delivering a modified version of the CASPR2 gene. When used to target sensory neurons, the gene therapy is envisaged to result in the overexpression of CASPR2 such that the CASPR2 polypeptide reduces the excitability of the targeted neurons by increasing the activity of potassium channels, bringing therapeutic benefit. In experimental models, the resultant overexpression of CASPR2 has so far yielded promising results and further studies are ongoing.

The invention is the subject of a PCT patent application, which is published as WO2018060712(A1), and resultant patent applications in the US and Europe are currently undergoing examination.

Licensing opportunity

Oxford University Innovation is now seeking a commercial partner to develop further and bring to market this potential new treatment for pain and epilepsy under an appropriate licence agreement.



For further information please contact:
Bob Fishleigh
bob.fishleigh@innovation.ox.ac.uk
+44 (0)1865 614429
www.innovation.ox.ac.uk
Project number: 13911

Technology Transfer from the University of Oxford

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Extracellular vesicle loading technology

Oxford researchers have developed a simple and effective technology for single step loading of extracellular vesicles for targeted drug delivery.

Extracellular vesicles

Extracellular vesicles (EVs), such as exosomes, are natural lipid vesicle nanoparticles secreted by cells, with important roles in intercellular communication and pathophysiology. As cells can naturally take up EVs from their surroundings, EVs have great potential as therapeutic drug carriers and delivery vehicles to transport drugs into specific cells and tissues. The inherent limitations of current strategies for loading EVs with molecules of interest are limiting industrial applications of EVs.

Issues to be addressed

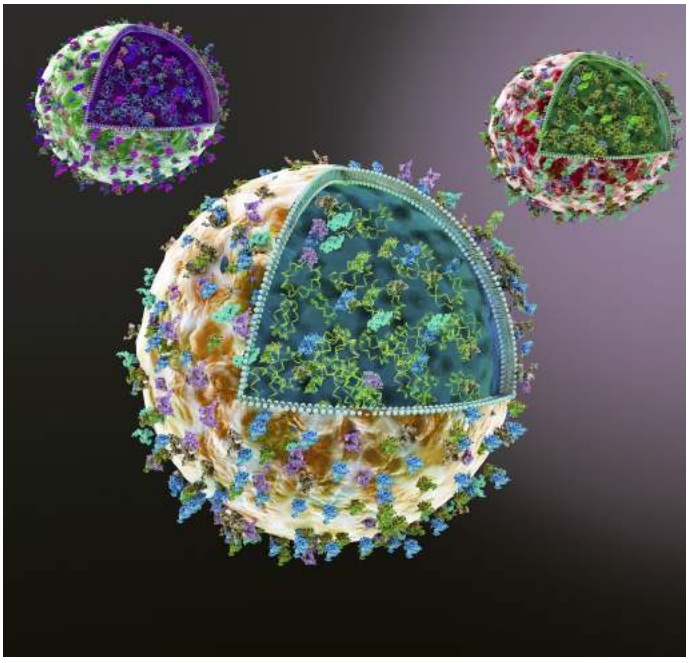
Current methods of loading therapeutic RNA into EVs Involves genetic manipulation of their host cells or chemical conjugation of peptides to EV surfaces. Both methods produce a heterogeneous population of EVs and are very labour intensive. Other methods such as electroporation and chemical transfection suffer from low loading efficiency. Vesicle aggregation is also one of the issues concerning bioavailability when administered to patients. Therefore, an efficient and reproducible method to load a specific molecule of interest into EVs remains an absolute unmet need to the industry.

Using the natural intercellular communication of EVs to improve drug delivery

Oxford academics have developed a simple and reproducible method to successfully load drug into EVs. This novel methodology, based on the presence of natural PS-binding sites on the surface of EVs, can be used with any type of EVs and does not require any genetic modification. PS-binding protein can be loaded directly with the molecules of interest or coupled with a second protein to capture other molecules of different chemical properties. Due to the universal presence of PS-binding sites on EVs, the method enables uniform and specific loadings of therapeutic molecules, such as DNA, RNA, protein and small molecule, into EVs, resulting in a homogenous population of EVs. The interaction identified also allows efficient and toxin-free purification of EVs by a solid support, such as a magnetic bead. Proof of concept study has demonstrated the successful delivery of siRNA in an animal model of neurodegenerative disease.

Commercialisation

This technology is the subject of a patent application currently pending. Oxford University Innovation is seeking industrial interest from parties wishing to licence and commercialise this technology.



For further information please contact:

enquiries@innovation.ox.ac.uk
+44 (0)1865 280830
www.innovation.ox.ac.uk
Project number: 15877

Technology Transfer from the University of Oxford

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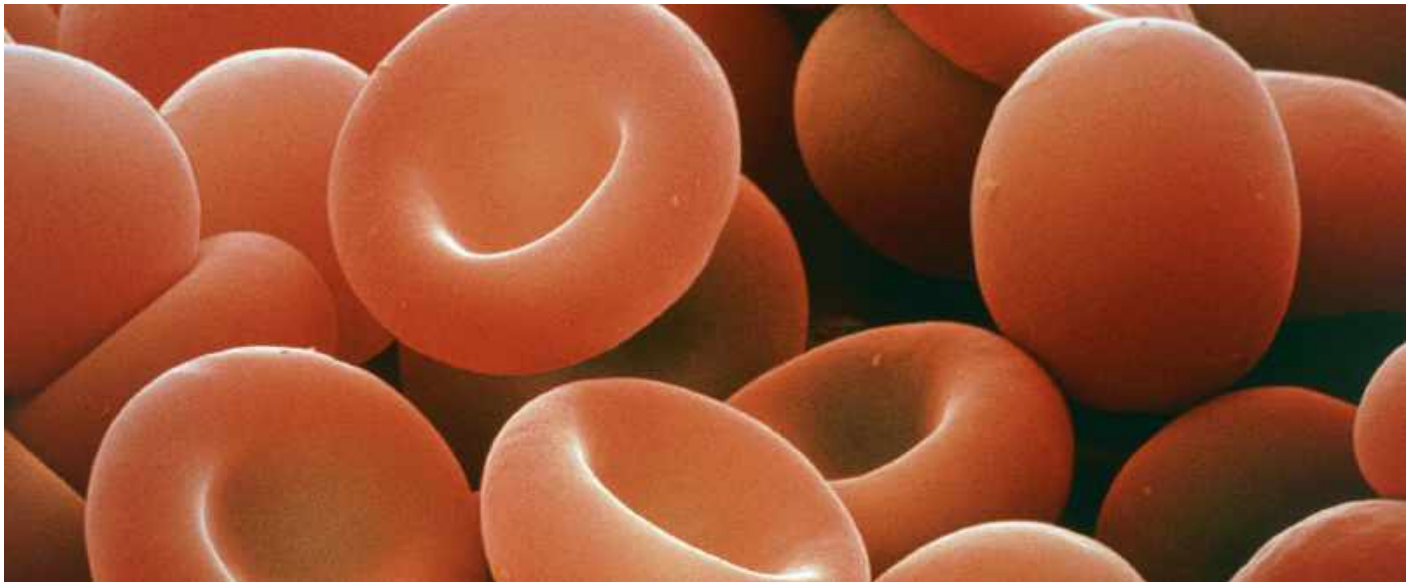
Base editing proteins to repair mutations in the haemoglobin gene

Oxford researchers have developed the use of programmable base editing proteins for gene editing therapy which offers a safer and effective approach to treat thalassaemia and sickle cell disease.



Beta thalassaemia

Beta thalassaemias are a group of inherited blood disorders caused by mutations in the human beta globin gene (HBB). This gene encodes one of the two chains of the haemoglobin molecule responsible for oxygen carriage by red blood cells.

Haemoglobin E (HbE) has a high prevalence in Asia because it confers protection against malaria. However, when this variant is inherited with a second beta thalassaemia mutation, severe thalassaemia can develop. This combination causes approximately 50% of all severe thalassaemia worldwide. This translates to ~20,000 births annually, who require lifelong blood transfusions every 2-3 weeks to survive.

Haemoglobin S (HbS) can result in sickle cell disease. This severe form of congenital anaemia results in life threatening complications. The median life expectancy with sickle cell disease is ~60 years in the UK at present but many patients die in their 40s from multiple complications.

Current treatment available

It is possible to cure sickle cell disease and severe thalassaemia in childhood with allogeneic bone marrow transplantation, but this carries a mortality rate of 1-5% and requires fully matched sibling transplant. Over the age of 18, allogeneic transplant would have an unacceptably high mortality.

Due to the risks of allogeneic transplantation it is only performed on a small percentage of patients with these conditions.

Oxford technology

The invention developed by researchers at the University of Oxford uses a programmable base editor to cure HbE and HbS beta thalassaemia.

The use of a programmable base editor is a safer and more effective approach to gene therapy than the addition of the HBB gene that could integrate into the genome at thousands of different sites.

The invention would allow the patient's own cells to be harvested, repaired ex vivo with the programmable base editor and then infused as part of an autologous bone marrow transplant. Autologous bone marrow transplants are much safer than an allogeneic transplant. It is likely the mortality would be <1% with such a procedure, even in adults with the disease.

This technology is subject to patent application WO2020/065303.

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: 16008

The information in this Project Profile is provided "as is" without conditions or warranties and Oxford University Innovation makes no representation and gives no warranty that it is the owner of the intellectual property rights in the technology described.

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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

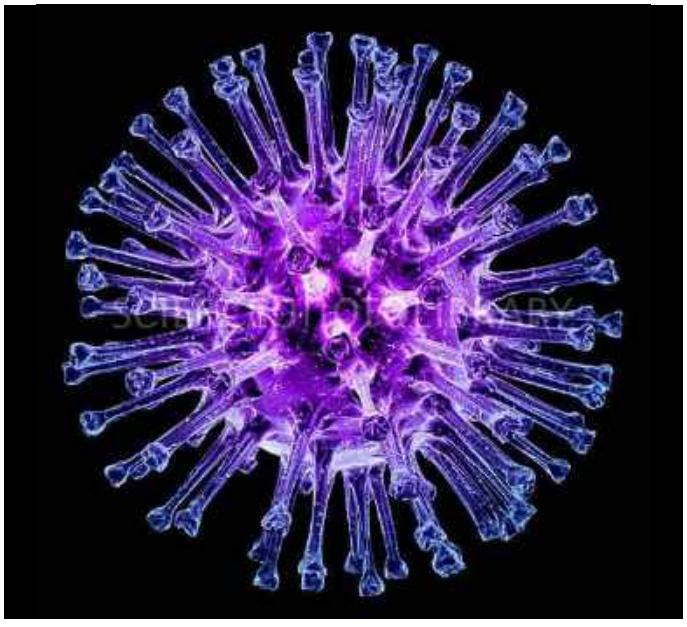
- Suppression of haemagglutinin signal sequence expression enables infection without replication
- Generates a T-cell mediated immune response shown to protect mice and ferrets from a broad range of type-A influenza strains
- Efficacy comparable to FluMist®, the best-in-class licensed live attenuated 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

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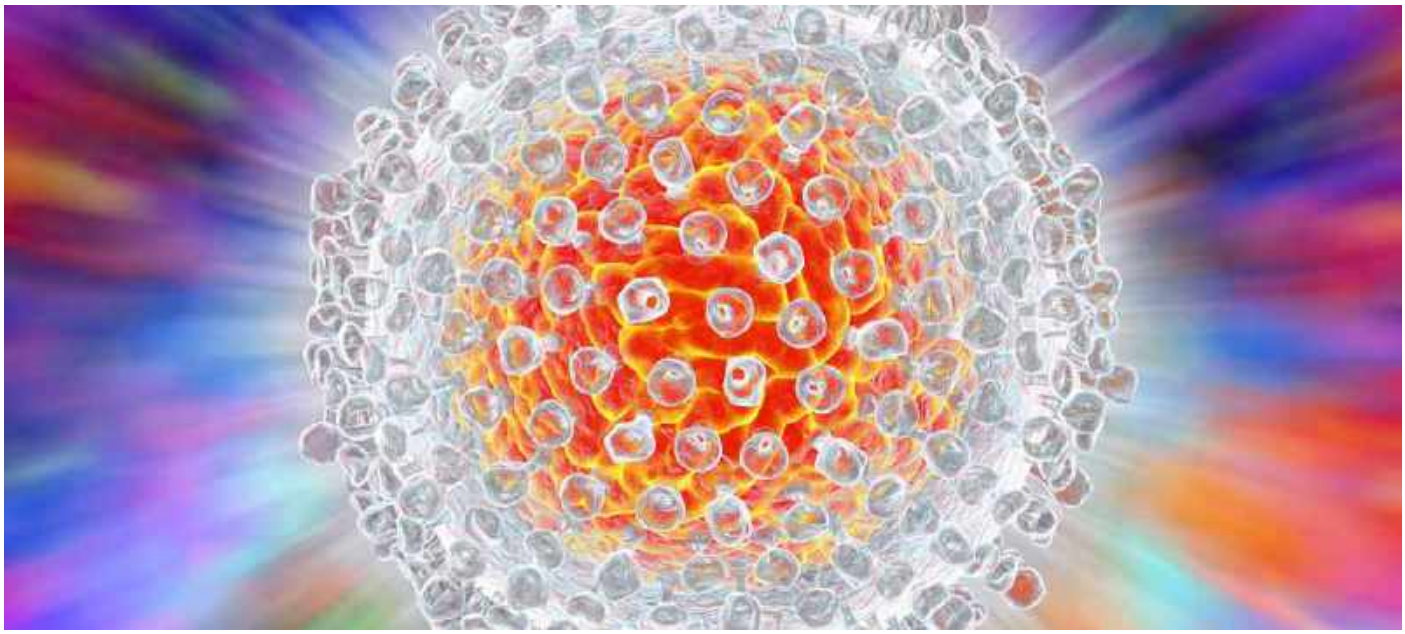
Hepatitis C Vaccine

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

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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.

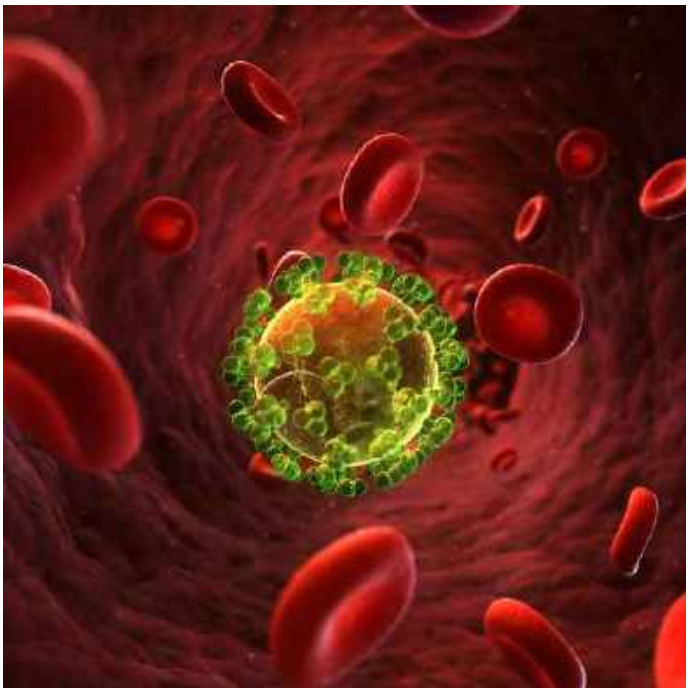
Administering the tHIVconsvX proteins as pairs using different vaccine modalities ensures a maximum match to global circulating HIV and the induction of effective, robust immunity.

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

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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

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A novel immunisation methodology

Available to license: A new “prime and target” immunisation methodology.

Oxford researchers have developed a novel, targeted approach to immunisation wherein a generalised T-cell response is initiated with a traditional-style vaccination route before the T-cells are subsequently targeted to a specific organ.

Immunisation

The process of immunisation has been carried out for centuries and has generally relied on the administration of an antigenic material, which stimulates an immune response, ultimately conveying systemic resistance to a specific pathogen. This has proven to be a highly effective methodology, resulting in the eradication of smallpox and the restriction of other diseases such as polio and tetanus. Despite these successes, this approach has fallen short when it comes to certain diseases, in particular, malaria.

Malaria

In 2015 malaria transmission was shown to be ongoing in 95 countries, putting 3.2 billion people at risk. In the same year, there were an estimated 214 million cases of malaria resulting in 438,000 deaths. There are currently no commercially available vaccines for malaria and prevention relies on several strategies such as vector control, anti-malarial medicines and physical precautions. Vaccines effective at preventing malaria are needed and have the potential to save millions of lives. The WHO recognises this and has published the Malaria Vaccine Technology Roadmap with the goal of licensing malaria vaccines by 2030.

Prime and Target

Researchers at Oxford have developed a new immunisation methodology which focusses on the localisation of the immune response resulting from vaccination. The first step involves the intramuscular administration of a recombinant adenovirus, which stimulates a T-cell response in an analogous fashion to a “classical” vaccine. Subsequent treatment with alternative routes of the same adenovirus localises the T-cells in the target tissue where the immune response is needed. This approach is highly effective when targeting the liver, resulting in a 100% efficacy against murine malaria.

Key advantages of this immunisation methodology:

- Outperforms current immunisation techniques
- Targeted to a specific organ system
- Highly effective against malaria
- Potential applications against other infectious diseases and cancer
- Both prophylactic and therapeutic immunisation possible

This novel approach has the potential to provide vaccines against a range of diseases, which currently pose a severe threat to public health.

Patent Protection

This technology is subject to patent application WO 2017/178809.

Oxford University Innovation is seeking external partners who wish to explore the use of this methodology for commercial applications.

https://pubmed.ncbi.nlm.nih.gov/30257955/

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: 13214

Technology Transfer from the University of Oxford

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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.

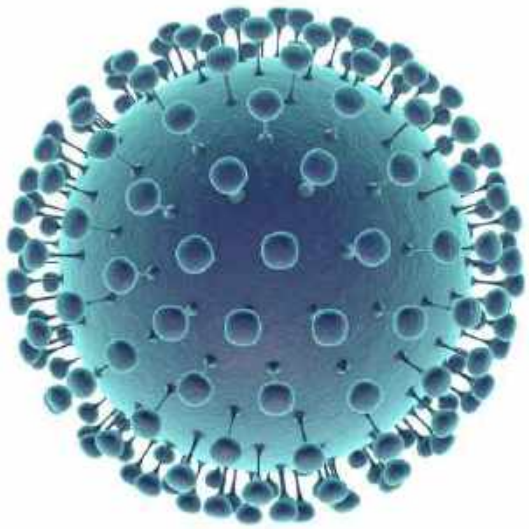
Zika viral vector vaccine

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

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Plasmid stabilisation for use in Shigella vaccine development

Oxford researchers have developed a method of plasmid stabilisation which is key to the development of a Shigella vaccine.

The global impact of Shigellosis

Species of *Shigella* are the leading cause of bacterial dysentery worldwide. *Shigella* bacteria invade the epithelium lining of the gut leading to diarrhoea and the clinical syndrome called shigellosis. Shigellosis particularly impacts young children living in low income countries. Despite significant reductions in mortality during the past few decades, there are still over 150,000 deaths per year attributable to shigellosis.

There is currently no vaccine available to prevent Shigellosis

Based on clinical severity, antibiotic resistance and disease burden, shigellosis caused by *Shigella* species is a prime target for vaccine development. The development of a *Shigella* vaccine would contribute significantly towards reducing the burden of disease, especially in nations where delivery of effective antimicrobials is challenging. To provide effective coverage, any vaccine developed should elicit protection against the most epidemiologically important *Shigella* serotypes, one of which is *S. sonnei*. This species is the most important serotype in industrialised counties and accounts for ~23% of disease isolates in less wealthy countries. A type III secretion system located on the plasmid pINV is critical for the virulence of *Shigella* bacteria. This plasmid is naturally maintained in growing bacterial populations through a process called post-segregational killing that consists of a toxin-antitoxin system.

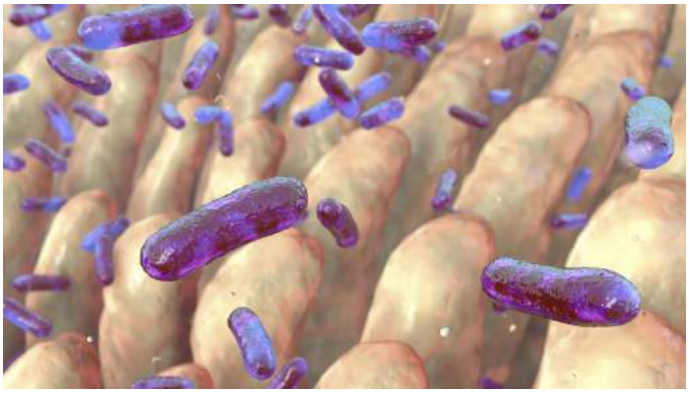
Unfortunately, growth of *S. sonnei* at 37°C in the laboratory results in loss of this plasmid with consequent loss of pathogen virulence. This reduces the effectiveness of a *Shigella* vaccine strain produced in the lab. Little is known about the mechanisms underlying the high rate of pINV plasmid loss in this pathogen.

Oxford researchers have developed a method to stabilise plasmid pINV

Researchers at the University of Oxford have developed a modified *Shigella* toxin-antitoxin system that super-stabilises the pINV plasmid in the bacterial host. This allows the construction of *S. sonnei* strains which retain their virulence in the lab. This will facilitate studies of host to pathogen interactions and future vaccine development. Additionally, this technique can be used to improve plasmid stability in other species of bacteria which could have significant use in development of other vaccines and for increasing the efficiency of biomanufacturing processes. The Oxford researchers have demonstrated that they can use the technique to increase the stability of low-copy number plasmids in *E. coli* which could significantly increase the efficiency of biomanufacturing proteins for therapeutic and other uses.

Intellectual property protection

Oxford University Innovation has filed a patent application based on 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: 14762

Technology Transfer from the University of Oxford

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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.

Formats available:

- Paper
- Telephone administered version

ALSAQ Users

The research, subsequent development and validation of the ALSAQ was supported by the UK's Motor Neurone Disease Association

Biogen

ALEXION

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

38 translations available

Find out more!

The Coeliac Disease Assessment Questionnaire (CDAQ)

Clinical Outcomes

The Coeliac Disease Assessment Questionnaire (CDAQ) is a 32-item, patient-reported outcome measure developed to investigate the health-related quality of life of people living with coeliac disease.

Background

The CDAQ was developed by researchers within the Health Services Research Unit, part of the Nuffield Department of Population Health at the University of Oxford.

There are two existing disease-specific PROMs that assess quality of life in people with coeliac disease, the Celiac Disease Questionnaire (CDQ) and the Coeliac Disease Quality of Life Survey (CD-QOL). However, there are limitations in the development of both measures, including the derivation of items. The CDAQ has been developed according to current best practice guidelines. The measure can be used in a range of settings, including clinical trials and clinical practice.

Development

1. Derivation of items

Qualitative interviews were conducted with 23 adults with coeliac disease. Variation was sought across participant's demographic and disease characteristics, particularly gender, age, and duration since diagnosis. Interview data was audio-recorded with the participant's consent and transcribed verbatim. Interview data was analysed thematically in NVivo9. Following analysis, 63 candidate items were developed.

2. Refinement of items

Experts, including health professionals and researchers, provided feedback on candidate items via individual interviews and an expert panel. Revisions to items were made based on their comments. Following revisions, ten cognitive interviews were conducted with adults with coeliac disease across two rounds, with revisions to the questionnaire occurring after each round. Interviews examined cognitive thought processes during questionnaire completion in order to identify sources of response error.
Finally, a translatability assessment was undertaken to assess the cultural and linguistic translatability of the questionnaire.

3. Item reduction and scale generation

A draft 51-item version of the CDAQ was completed by 412 people with coeliac disease. Nineteen items were removed following data analysis. A principal components analysis (with Varimax rotation) was conducted on the remaining 32 items, identifying six meaningful dimensions, two of which were merged. Cronbach's alpha values ranged between 0.82 and 0.88 for all dimensions, indicating good internal consistency.

4. Evaluation of psychometric properties

The CDAQ was completed by a further 268 people in order to evaluate the psychometric properties of the measure. The final CDAQ contains 32 items addressing the five dimensions below. It measures health-related quality of life using a recall period of the past four weeks.
stigma (8 items)
dietary burden (8 items)
symptoms (5 items)
social isolation (5 items)
worries and concerns (6 items).
A study to assess the CDAQ's responsiveness to change is currently underway.

Scoring System

Dimension scores and an overall index score can be calculated for the CDAQ. Raw scores are transformed to a 0-100 scale, where 0 is the poorest quality of life as measured by the CDAQ, and 100 is the highest quality of life as measured by the CDAQ.

Apply to use

The CDAQ 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:

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5 translations available

Find out more!

The Diabetes Health Profile

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:

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New

Short form (3 + 5 item) utility weighted versions for calculation of QALYs now available!

39 translations available

Find out more!

Duchenne Muscular Dystrophy Quality of Life Measure (DMD QoL)

Clinical Outcomes

The DMD QoL is the first condition-specific preference-based measure of health-related quality of life (HRQoL) in people with Duchenne Muscular Dystrophy (DMD).

Background

The DMD QoL can be used in cost-effectiveness evaluations of new healthcare interventions. It is the product of a study which featured input from a multidisciplinary team working with the charity Duchenne UK, clinicians, patients and primary caregivers of people with DMD.

The DMD QoL is a 14 item questionnaire available as a patient reported version and a proxy version.

Funding

This work was supported by Duchenne UK under the Project Hercules funding stream.

Scoring

The DMD-QoL has a hierarchical (or 'higher-order') factor structure, with 3 lower-order factors (physical, social, and psychological) and 1 higher-order factor (overall quality of life [QoL], comprised of the 3 lower-order factors).

A simple, summative scoring system is proposed for each of the 3 lower-order factors, and consequently the higher-order factor (QoL) being a composite score of these.

Higher scores represent a more positive QoL (overall or within each subscale).

Apply to use

The DMD-QoL 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:

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29 translations available

Find out more!

Diabetes Self Management Technology Questionnaire (DSMT-Q)

Clinical Outcomes

The Diabetes Self-Management and Technology Questionnaire (DSMT-Q) is a patient reported measure that has been developed to assess self-management among people living with type 2 diabetes

Background

Available to use in two versions (web-based and mHealth technologies users and non-users).

The DSMT-Q includes 13 questionnaire items over two sub-scales. Understanding individual health and making informed decisions (7 items) and Confidence to reach and sustain goals (6 items).

The DSMT-Q has been developed with both patient and expert input and can be used in a range of applied settings. Whilst the questionnaire has been designed to ensure relevance to people living with type 2 diabetes who are using web-based and mHealth technologies, items are also applicable to those who are not using technology to manage their health. As such, this instrument may be used in a variety of contexts where a comparator group receives standard care or non–technology-based resources.

This tool is fully compliant with relevant regulatory bodies, such as the FDA and EMA and has shown good psychometric properties.

Design & Development

The content of the DSMT-Q was informed by an initial study that undertook in-depth qualitative interviews (n=15) with people living with type 2 diabetes in order to explore experiences of using web-based and mHealth technologies to manage their health. On completion of the interviews, 36 items were developed and refined following cognitive debrief interviews with people living with type 2 diabetes, expert consultation, and public patient involvement (PPI) feedback. Item reduction steps were performed on survey data (n=250), and psychometric validation of the remaining candidate items using appropriate quantitative methods were carried out.

The two subscales identified via the study show high construct validity, internal consistency and test-retest reliability. The validation phase was conducted entirely via electronic COA means (eCOA).

Scoring

A scoring guide is available for researchers. This includes sub scale calculations. Individual item responses are coded from 0-4 with a score ranging from 0 to 100 where a lower score indicates lower self-management.

Delivery Methods

Available to use in two versions (web-based and mHealth technologies users and web-based and mHealth technologies non-users), for electronic completion.

Complimentary Measures

Due to its focus on the use of technology to aid self-management, the DSMT-Q can be usefully integrated with other measures of self-management or quality of life for people with type 2 diabetes. In our portfolio, for instance, the HASMID, a mixed health related quality of life and self-management instrument, and the DHP, which measures the impact of diabetes 1 and 2 on the behaviour and psychology of patients.

Apply to use

The DSMT-Q is managed, as part of a wide portfolio of Clinical Outcome Assessments, 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:

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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.

Formats available:
- Paper - Telephone administered version

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:

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58 translations available

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:

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New

Preference-based utility tool used to extract health economic data from the existing HASMID-10, now available!

Find out more!

Long-Term Conditions Questionnaire (LTCQ)

Clinical Outcomes

The LTCQ was designed and developed to understand the impact of long-term health conditions on people's lives, and to find out what support those people want or need

Background

A long-term condition (LTC) is any health issue that has lasted, or will last, for at least 12 months. LTCs include memory problems, depression and other mental health conditions as well as physical health conditions such as diabetes and heart disease. The LTCQ is a patient-reported outcome measure for assessing the overall impact of living with long-term health conditions, including multi-morbidity.

Design & Development

The LTCQ was designed and developed by researchers at the Health Services Research Unit (HSRU) at the University of Oxford and the Personal Social Services Research Unit at the University of Kent, with support by the Department of Health (Policy Research Programme) and NIHR (CLAHRC Oxford).

An initial conceptual framework was developed through a review of the literature and in-depth interviews with professional stakeholders.

The 20 items of LTCQ were developed through in-depth patient interviews to generate content, and items were refined with lay and professional stakeholders. A translatability assessment was conducted to further refine the items.

A larger-scale validation study among primary care and social care recipients (n=1200+) in England demonstrated the LTCQ's measurement reliability and validity of its broad construct, 'living well with LTCs'. A second study validated the LTCQ in people with memory problems recruited through memory clinics.

The LTCQ encompasses traditional domains of PROMs (e.g. role functioning, social participation) as well as domains that have more recently emerged as important for living well with LTCs (e.g. treatment burden, confidence to self-manage illness).

Further Validation

The researchers are continuing the validation of the LTCQ for specific patient cohorts such as dementia and mild cognitive impairment. Please contact us for updates and further details.

Scoring

Scoring the LTCQ is a very straightforward of the summation of individual item scores, with higher scores indicating higher health-related quality of life. Further guidance is available.

Delivery Methods

The LTCQ is to date, validated for pen and paper completion. Careful migration to a digital delivery format (for example screen based device) can be authorised. Please contact us for advice.

Funding

The initial and ongoing research of the LTCQ is funded by NIHR as part of the Collaboration for Leadership in Applied Health Research and Care (CLAHRC) – Oxford. The Oxford team collaborated with the Quality and Outcomes of person-centred care policy Research Unit (QORU) at the University of Kent.

NHS
National Institute for Health Research

Apply to use

The LTCQ is managed, as part of a wide portfolio of Clinical Outcome Assessments, 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:

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3 translations 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:

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Find out more!

MAAQ
Mathematics Attitudes and Anxiety Questionnaire

Mathematics Attitudes and Anxiety Questionnaire (MAAQ)

OXFORD UNIVERSITY INNOVATION
UNIVERSITY OF OXFORD
Clinical Outcomes

A substantial number of children and adults have mathematics anxiety, which may severely disrupt their mathematical learning and performance, both by causing avoidance of mathematical activities and by overloading and disrupting working memory during mathematical tasks. Maths anxiety is a relatively frequent phenomenon and often related to dyscalculia.

Background

A number of research papers lay out the issues of attitudes to and anxiety with mathematics: –

Mathematics depends not only on cognitive abilities but also on emotional factors and attitudes

Emotional factors may play a large part in mathematical performance, with mathematics anxiety playing a particularly large role

Mathematics anxiety might influence performance more directly, by overloading working memory

Relationships between mathematics anxiety and performance may also be in the other direction. Poor mathematical attainment may lead to mathematics anxiety, as a result of repeated experiences of failure, potentially leading to a vicious circle, where anxiety and performance affect each other negatively

Development of mathematics anxiety is likely to be due both to social factors, such as exposure to teachers who themselves suffer from mathematics anxiety, and to pre-existing difficulties in numerical cognition; and that those with initial mathematical difficulties are also likely to be more vulnerable to the negative social influences

Thus, a standardised instrument to detect math anxiety as early as possible and monitor at regular intervals would be useful. The Mathematics Attitudes and Anxiety Questionnaire (MAAQ) has been designed, tested, developed and shown to be a simple to complete assessment of attitudes and anxiety related to the individual (respondents) view of mathematics.

The PRO

The MAAQ uses age-appropriate, simple to understand, pictorial rating scales to capture the student / child's personal views. The MAAQ is an Interviewer administered questionnaire. Responses are captured during an interview by a teacher, teaching assistant, SEN team member, parent or carer who records the responses. The MAAQ consists of 28 questions, focused on 7 domains of measuring the respondents view of mathematics:

1. maths in general
2. written sums
3. mental sums
4. easy maths
5. difficult maths
6. maths tests and
7. understanding the teacher

Each of the seven domains has 4 questions associated with it. For each domain, children were asked about their:-

1) Self-rating ('How good are you?') on a scale consisting of ticks and crosses ('very good' to 'very bad');

2) Liking for the items ('How much do you like it?'); on a scale consisting of sweets and wasps ('like very much' to 'hate very much');

3) Anxiety about them ('How worried would you feel?') on a scale of facial expressions ('very relaxed' to 'very worried') and

4) Unhappiness at poor performance ('How unhappy would you feel if you did badly?') on a scale consisting of faces with frowning or happy faces ('very unhappy' to 'very happy')

The MAAQ 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**

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Find out more!

The Mild Cognitive Impairment Questionnaire (MCQ)

Clinical Outcomes

The Mild Cognitive Impairment Questionnaire (MCQ) is a self-report, 13-item PRO developed to assess quality of life (QoL) in people with mild cognitive impairment (MCI).

Background

The MCQ is the first PRO measure to be developed specifically to assess QoL in people with MCI. The MCQ taps into two domains of patient reported quality of life, namely Emotional Effects (6 items) and Practical Concerns (7 items). The MCQ is available as a self-report measure, but can also be accompanied by an advocate / carer's version (separate 14 items) of the measure.

The development of the MCQ closely followed FDA guidance (on the development of PRO measures for use in supporting label claims, FDA, December 2009) where possible.

The MCQ has been developed so it can be used to assess outcomes following intervention such as cognitive rehabilitation or potential pharmacological therapies for MCI. It is a short, simple assessment tool (taking only about 5 minutes to complete) for use in a variety of clinical and research settings to assess the effect of interventions for people with MCI. The MCQ could theoretically be applied to mild dementia but this application has not been validated yet.

Development

The MCQ was developed and tested in a comprehensive three stage process:

Stage 1 – Item generation.
Semi-structured, in-depth interviews were carried out with 23 people recently diagnosed with MCI. A set of preliminary questionnaire items were then discussed with an expert panel and refined to produce a draft questionnaire. The draft questionnaire was then discussed with a focus group of 11 people with MCI resulting in a final draft 17-itme questionnaire.

Stage 2 – Item reduction and scale generation.
A first postal study (n=280, resulting in 146 completed questionnaires) was conducted using the 17 item questionnaire generated at stage one, along with the SF-12 v2 (Mental Health Component Summary Score (MCS) and Physical Component Summary Score (PCS)). The resulting data was analysed to identify any issues with items measuring the same concept and assess internal consistency (using Cronbach's alpha) of each domain. Construct validity of the MCQ was examined by correlation with the SF12 results. Four items were removed because of floor effects. Factor analysis identified two domains of Emotional Effects (irritation/frustration, anxiety, low mood, concern about the future, worry about the reactions of others and worry that their memory problems) and Practical Concerns (worry about: having forgotten things e.g. names, plans or appointments, problems with conversation due to memory difficulties, feeling generally 'slowed down' or less independent and concern about upsetting others).

Stage 3 – Testing validity.
The construct validity of the MCQ was examined by correlation with the SF-12v2 MCS and PCS and shown to be adequately correlated.
Further information on the design, development and testing of the MCQ is available in the development paper – see key references. The methods used to develop the MCQ were adopted as they have been shown to be effective in the development of similar questionnaires in the past and in many areas are compliant with FDA guidance in the development of PRO measures.

Scoring

The 13-item MCQ provides scores for each of the 2 domains. Alternatively, the sum of the scores can provide a single figure used to assess the overall health-related quality of life profile of the individual questioned.

Apply to use

The MCQ 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:

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3 translations available

Find out more!

Manchester Foot Pain and Disability Index (MFPDI)

The Manchester Foot Pain and Disability Index (MFPDI)

OXFORD UNIVERSITY INNOVATION

UNIVERSITY OF OXFORD

Clinical Outcomes

The Manchester Foot Pain and Disability Index (MFPDI) is a Patient Reported Outcome (PRO) measure developed and validated to measure pain specifically related to a foot disability. The MFPDI is a suitable instrument for assessing the impact of painful foot conditions in community and clinical populations.

Background

The MFPDI was the first foot related pain measure to incorporate the views of people with known foot problems from the early stages of development. This self-administered PRO has been validated for use among patients of varying levels of disability associated with a specific foot or general medical condition.
The MFPDI was designed and developed by researchers at the University of Manchester

The PRO

The MFPDI is a self-administered, paper based PRO consisting of 19-items assessing foot pain and disability. The PRO contains three constructs (four subscales) which reflect disabilities associated with foot pain and two additional items relating to work and leisure. The three constructs identified within the MFPDI are:
- Functional limitation (10 items)
- Pain intensity (7 items)
- Personal appearance (2 items)
- Responses are recorded on a three point scale:
- None of the time
- On some days
- On most /every day(s)

Attributes

Valid
The MFPDI has been repeatedly shown to demonstrate content, construct and criterion validity amongst people with varying levels of foot problems.

Reliable
The MFPDI exhibits good internal consistency.

Sensitive
The MFPDI has demonstrated its ability to discriminate between known groups with varying levels of a foot specific disability within both clinical and population settings.

Ease of use
The MFPDI is quick and easy to complete, administer and score.

Example studies

van der Zwaard BC, Elders PJ, Knol DL, Gorter KJ, Peeraer L, van der Windt DA, van der Horst HE. Treatment of forefoot problems in older people: study protocol for a randomised clinical trial comparing podiatric treatment to standardised shoe advice. J Foot Ankle Res. 2011 Mar 31;4(1):11.

Roddy E, Muller S, Thomas E. Onset and persistence of disabling foot pain in community-dwelling older adults over a 3-year period: a prospective cohort study. J Gerontol A Biol Sci Med Sci. 2011 Apr;66(4):474-80. Epub 2010 Nov 24.

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Bowen CJ, Edwards CJ, Hooper L, Dewbury K, Sampson M, Sawyer S, Burridge J, Arden NK. Improvement in symptoms and signs in the forefoot of patients with rheumatoid arthritis treated with anti-TNF therapy. J Foot Ankle Res. 2010 Jun 17;3:10.

Apply to use

The MFPDI 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

13 translations available

Find out more!

The Myocardial Infarction Dimensional Assessment Scale (MIDAS)

MIDAS-35

Clinical Outcomes

The Myocardial Infarction Dimensional Assessment Scale (MIDAS) is a PRO measure developed and validated to specifically measure the health status of individuals who have suffered a myocardial infarction (MI).

Background

The MIDAS was designed and developed from the collaboration between PRO experts at Oxford (Professor Crispin Jenkinson) and the University of York (Professor David Thompson, now at ACU Melbourne, and Mr Alun Roebuck). The MIDAS was created as existing quality of life instruments lacked sensitivity to change in assessing health status in MI patients.

The PRO

The 35-item MIDAS was designed and developed to be able to measure dimensions of specific importance to MI patients and be sensitive to change in health status. The resulting MIDAS is applicable to drug development or other interventions, including cardiac rehabilitation. These interventions are known to have an impact on longevity, and yet, until the development of the MIDAS, their impact on health related quality of life, from the patient's perspective, remained unknown.

Attributes

Validated
For use in patients in the early recovery period following MI and in the long term.
Sensitive to change in health status
The MIDAS can readily be used to measure the outcome of any therapeutic intervention.

Reliable
Results show that the MIDAS is highly reliable, both in terms of internal reliability at the patient group level and, given the magnitude of the reliability results, potentially at the individual level.

Content
The MIDAS contains seven dimensions (physical activity; insecurity; emotional reaction; dependency; diet; concerns over medication; side effects) and so addresses a combination of concerns distinctively associated with MI patients.

Condition specific
Addresses aspects of MI not covered by generic PROs.

Easy to use
Short and simple in format, so that it is applicable in a wide range of healthcare applications and results in high response rates. Although predominantly used as patient self-complete questionnaire the MIDAS can be interviewer administered.

Development

The MIDAS was designed and developed using methods consistent with best-practice in PRO instrument development:
1. Literature review,

2. Exploratory in-depth interviews with MI patients, until no new significant themes appeared,

3. Item generation – of a large pool of candidate questionnaire items (48 items),

4. Item reduction and scale generation – A postal survey (410 individuals with MI) was conducted to determine the acceptability of the measure. This step also enabled the development of a shorter, and more practical, instrument with fewer items, as well as the identification of sub-scales within the instrument,

5. Assessment of construct validity – A Follow up survey was undertaken to test the validity of the questionnaire in comparison with the SF-36, two clinical measures of outcome and a physical health assessment by a specialist cardiac nurse.

Apply to use

The MIDAS 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

8 translations available

Find out more!

Manchester Oxford Foot Questionnaire (MOxFQ)

The Manchester-Oxford Foot Questionnaire (MOxFQ)

OXFORD UNIVERSITY INNOVATION | UNIVERSITY OF OXFORD

Clinical Outcomes

The Manchester-Oxford Foot Questionnaire (MOXFQ) is a 16-item Patient Reported Outcome (PRO) measure developed and validated for use in studies assessing outcome following foot and/or ankle corrective surgery.

Background

Foot and ankle surgery accounts for approximately one fifth of orthopaedic practice and has a high level of patient dissatisfaction. The Manchester-Oxford Foot Questionnaire's (MOxFQ's) are 16-item Patient Reported Outcome (PRO) measures developed and validated for use in clinical trials involving foot surgery. These self-administered PROs assesses how foot problems impair health-related quality of life can be completed before and after surgery.

The original MOxFQ (foot) PRO was developed as an outcome measure of hallux valgus (bunions) corrective surgery and has recently been slightly amended and validated for use among patients with a variety of foot or ankle problems. The **MOxFQ (foot)** and the **MOxFQ (foot and ankle)** PROs are available for license through Clinical Outcomes.

The MOXFQ PROs were developed by researchers in the University of Oxford using interviews with patients and partially drawing on a pain related foot disability measure, the Manchester Foot Pain and Disability Index (MFPDI), as a template for item generation and content. The MFPDI is also available through Clinical Outcomes.

Advantages

The MOXFQ PROs are self-administered, paper based measures consisting of 16-items. The PROs measure three domains:

1. Walking/standing (7 items)
2. Pain (5 items)
3. Social interaction (4 items)

Response options consist of a 5 point Likert scale ranging from no limitation to maximum limitation.

Developers' of the PROs recommend using the MOXFQ (foot) questionnaire for clinical trials that are specifically investigating outcomes of interventions for hallux valgus correction and use of the MOXFQ (foot and ankle) in all other instances. For example, trials of surgery or audits of outcomes involving all other foot or ankle condition (this may include people with hallux valgus).

Scoring System

Scores for each domain are calculated by summing the responses to each item within a given domain. Raw scores can be converted to a 0-100 metric where 100=most severe. As mentioned above, the domains can also be summed to give a Summary Index score.

Attributes

1. Valid
2. Reliable
3. Ability to detect change
4. Acceptable
5. Undimensional scaling

The MOxFQ is endorsed by the British Foot and Ankle Society to measure surgical outcome.

Apply to use

The MOxFQ 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:

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14 translations available

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).

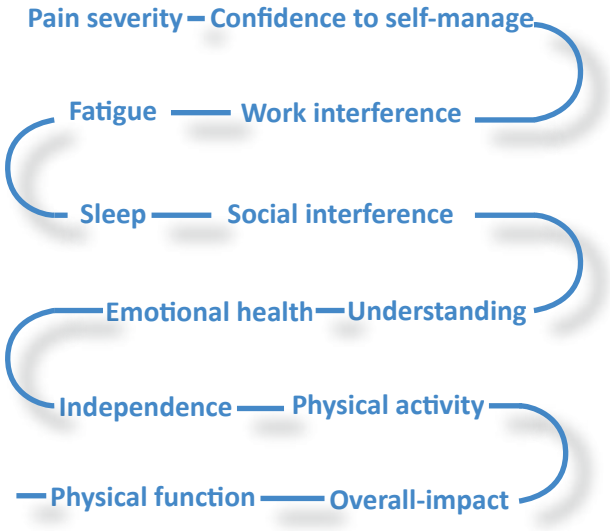
The Versus Arthritis MSK-HQ contains 14 items and measures the health status in patients with MSK conditions over the past two weeks. MSK-HQ was developed as a collaboration between Keele and Oxford Universities.
The development of MSK-HQ was supported by Versus Arthritis and the NHS.

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:

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+44 (0) 1865 614480

10 translations available

Find out more!

Oxford Arthroplasty Early Change Score (OACS)

Clinical Outcomes

The Oxford Arthroplasty Early Change Score (OACS) is a 14 question Patient Reported Assessment measure used to assess change, recovery pathways and interventions during the first six weeks following surgery

Background

Lower limb arthroplasty is a commonly performed procedure for symptomatic end-stage arthritis which has not responded to conservative medical treatment.

Each patient's perspective of the surgical process and early recovery period impacts on their quality of life.

The OACS was devised to gain deeper understanding of the patient perspective on their treatment in the perioperative period and can be used to assess change, recovery pathways and interventions during the first six weeks following surgery.

The Oxford Arthroplasty Early Change Score (OACS) is a 14 question Patient Reported Assessment measure developed by researchers at the Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences and Nuffield Department of Population Health at the University of Oxford. It was designed and developed in accordance with FDA guidelines (2009) and sector best practices. It is validated for use in the first six weeks following Unicompartmental knee arthroplasty (UKA), Total knee arthroplasty (TKA) and Total hip arthroplasty (THA).

The good measurement properties of the OACS, its relevance to patients, clinicians and other stakeholders, make it the ideal measurements for use in randomised controlled trials that assess the efficiency of different interventions in this patient population.

"As surgeons, once our patients are discharged from our care following surgery, they enter a black hole where we lose sight of how they are progressing with their new hip or knee. The OARs and OACs are the assessment tools by which we can now monitor those patients that were previously invisible to us in the days and weeks immediate-

Funding

The development of the OACS was funded in part by Sigma Theta Tau International Honor Society of Nursing.

Scoring

A scoring guide is available specifically for OACS and details how to score the change measure across a range of 100, with minus 50 being much worse than before surgery, to 50, being much better than before surgery. Zero indicates no change from self-reported preoperative health status. It also recommends how to treat missing responses.

Complementary Measures

The OACS can be used with an early recovery tool, the Oxford Arthroplasty Early Recovery Score (OARS), a Patient Reported Outcome Measure developed under the same guidelines and applicable to the same patient population. The two measures give a snapshot of both patient perceived outcomes at the time taken and also improvement, or change, since the surgery.

The OACS can also be used as an 'acute' perioperative measure of recovery in combination with the Oxford Hip and Knee Scores, with their longer term recall periods.

Apply to use

The OACS 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:

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Find out more!

The Oxford Arthroplasty Early Recovery Score (OARS)

Clinical Outcomes

The Oxford Arthroplasty Early Recovery Score (OARS) is a 14-item Patient Reported Outcome measure for use in assessing recovery pathways and interventions in arthroplasty

Background

Lower limb arthroplasty is a commonly performed procedure for symptomatic end-stage arthritis which has not responded to conservative medical treatment. Each patient's perspective of the surgical process and early recovery period impacts on their quality of life. The OARS is a brief, easy-to-use measurement tool for use in assessing recovery pathways and interventions in arthroplasty. It taps into patients feeling around four domain: Pain, Sleep, Nausea and feeling unwell,
Mobility. It was devised to gain deeper understanding of the patient perspective on their treatment in the perioperative period and can be used to assess change during the first six weeks following surgery.

The Oxford Arthroplasty Early Recovery Score (OARS) is a 14-item Patient Reported Outcome measure
developed by researchers at the Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences and Nuffield Department of Population Health at the University of Oxford. It was designed and developed in accordance with FDA guidelines (2009) and sector best practices. It is validated for use in the first six weeks following Unicompartmental knee arthroplasty (UKA), Total knee arthroplasty (TKA) and Total hip arthroplasty (THA).

"As surgeons, once our patients are discharged from our care following surgery, they enter a black hole where we lose sight of how they are progressing with their new hip or knee. The OARs and OACs are the assessment tools by which we can now monitor those patients that were previously invisible to us in the days and weeks immediately following hip or knee replacement surgery." – **Professor Oliver Pearce, FRCS, Consultant Trauma and Orthopaedics**

Funding

The development of the OARS was funded in part by Sigma Theta Tau International Honor Society of Nursing.

Scoring

A scoring guide is available specifically for the OARS and details how to score the change measure across a range of 100, with 0 being poor recovery, to 100 being positive and indicative of a good recovery. The guide also addresses scoring the separate domains (Pain and Nausea and feeling unwell; Fatigue and Sleep and Increasing function and mobility. It also recommends how to treat missing responses.

Complementary Measures

The OARS can be used with an early change assessment tool, the Oxford Arthroplasty Early Change Score (OACS), a Patient Reported Assessment Measure also developed under the same FDA guidelines and applicable to the same patient population. 'The two measures give a snapshot of both patient perceived outcomes at the time taken and also improvement, or change, since the surgery.

The OARS can also be used as an 'acute' perioperative measure of recovery in combination with the Oxford Hip and Knee Scores, with their longer-term recall periods

Apply to use

The OARS 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:

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+44 (0) 1865 614480

Find out more!

Oxford Cognitive Screen

The Oxford Cognitive Screen (OCS)

Clinical Outcomes

Up to now, no short efficient cognitive screening tool was available that targets stroke survivors. The OCS (Oxford Cognitive Screen) can be delivered at the bedside in acute stroke, is easy to administer and score and is inclusive for patients with aphasia and neglect. It returns a visual snapshot of a patient's cognitive profile which summarizes performance across 5 cognitive domains.

Background

The Oxford Cognitive Screen brings neuropsychological expertise to cognitive screening in (sub)acute stroke, where long domain specific assessments are not practical due to time and staff pressured environments. The OCS is a short yet informative, domain-specific and Aphasia & Neglect friendly screening tool that particularly picks up and evaluates prevalent post stroke cognitive impairments such as hemispatial neglect, apraxia, and problems in reading and writing.

The OCS, as a domain-specific cognitive screen results in a cognitive profile, highlighting areas of impairment as well as preserved cognitive abilities to give a more informative outcome than an overall 'cognition pass/-fail'.

The PRO

The Oxford Cognitive Screen is a short and efficient cognitive screening tool that can be delivered at the bedside in acute stroke.

The OCS is easy to administer and score and importantly is inclusive for patients with aphasia and neglect. OCS returns a visual snapshot of a patient's cognitive profile, in a 'wheel of cognition', which at a glance demonstrates the specific cognitive domain impairments in:

- Attention
- Language
- Praxis
- Number
- Memory

No specific training outside the manual and online tutorial video is required to administer OCS, though we are happy to help set up local hands-on training courses.

Development

The OCS was developed, normed and validated at the University of Oxford, the endorsed translations of OCS available adhere to a high standard and have been normed and validated for the targeted population. The OCS is freely available for publicly funded clinical and research use.

Administration

No courses or specific in person training is required to administer OCS. We recommend reading the manual and scoring guides as well as watching a demonstration video in the first instance that is available on our website.

As with any other assessment, practice makes perfect, and you will improve in fluency and speed, particularly in anticipating the next question/task and being able to move the relevant pages around and swap between the test booklet, the examiner scoring page and the pages for the participant to draw/write on.

Apply to use

The OCS 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

15 translations available

Find out more!

The Oxford Depression Questionnaire (ODQ)

Clinical Outcomes

The Oxford Depression 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

17 translations available

Find out more!

The Oxford Elbow Score (OES)

Clinical Outcomes

The Oxford Elbow Score (OES) is a short 12-item PRO specifically designed and developed for assessing outcomes of elbow surgery.

Background

The PRO was designed and developed by researchers within the Health Services Research unit, part of the Nuffield Department of Population Health at the University of Oxford, in association with surgical colleagues at the Nuffield Orthopaedic Centre.

The OES, which is the only patient-reported PRO for elbow surgery in existence, has been tested in a surgical context with patients and shown to be reliable, valid and responsive.

The PRO

There are 12 questions in the Oxford Elbow Score with three unidimensional domains:

- Elbow function
- Pain
- Social-psychological

Each of the domains comprises 4 items with good measurement properties. Each of the domains/sub-scales was identified by Factor analysis and shown to be unidimensional by Rasch analysis. In addition each scale has been demonstrated to have good internal reliability using Cronbach's alpha.

Attributes

- A condition-specific PRO designed and developed specifically for use in assessing the outcome of surgical intervention of the elbow;
- Can be used as an indicator for recovery and general improvement in quality of life following surgery on the elbow;
- Shown to be valid, reliable and sensitive to change after rigorous testing;
  Brief and easy to complete resulting in good return rates;
- Can be completed anywhere and delivered by post, making follow-up of large numbers of patients much more feasible (and cheaper) than conducting clinical assessments;
- Easy to interpret scores;
- 3 subscales/domains capture patient views on their elbow and the impact on quality of life;
- Application of the OES could be extended to the assessment of other (non-surgical) forms of therapy, for example physiotherapy.

Development

The development of the OES was driven by demands for a suitable PRO by orthopaedic surgeons who wished to measure the outcomes of their treatments from the patient's perspective.

Example studies

The OES is primarily used to assess outcomes of elbow surgery including total elbow replacement and arthroscopic surgery. Other uses of the OES include:
Assessment of patient outcomes following alternative non-surgical interventions, including physical therapy, cortisone injections, joint supplements and anti-inflammatory medications

Orthopaedic products companies have used the OES to optimise their products and associated surgical procedures in order to improve patient outcomes from surgeries employing their products

Public and private healthcare providers have used the OES to assess patient outcomes across multiple facilities as a measure of the performance of individual treatment centres, which can be used to identify high-performing centres and to raise standards through sharing best practices

For further information about the measure or how to apply for a licence please get in touch via:

healthoutcomes@innovation.ox.ac.uk

+44 (0) 1865 614480

16 translations available

Find out more!

The Oxford Hip Score (OHS)

Clinical Outcomes

The Oxford Hip Score (OHS) is a short 12-item patient-reported PRO specifically designed and developed to assess function and pain with patients undergoing hip replacement surgery. It is short, reproducible, valid and sensitive to clinically important changes.

Background

The OHS was designed to be completed by the patient thus minimizing potential bias unwittingly introduced by surgeons when assessing the results themselves.

The PRO was designed and developed by researchers within the Nuffield Department of Population Health at the University of Oxford in association with surgical colleagues at the Nuffield Orthopaedic Centre.

Development

Prior to the development of the OHS, only crude measures of surgical failure, such as the need to perform revision surgery, had been employed in the assessment of patient outcomes. The development of the OHS was driven by the need to conduct more systematic and accurate monitoring of patient outcomes following THR.

Formats available:

- Paper
- Telephone administered version

The PRO

The OHS is a patient self-completion PRO containing 12 questions on activities of daily living. The OHS has been developed and validated specifically to assess function and pain for patients undergoing total hip replacement (THR) surgery. The OHS is the most evaluated hip specific measure available.

Example studies

The Oxford Knee Score and the Oxford Hip Score (OHS) have been adopted by the UK Department of Health (DoH) for the assessment of approximately 120,000 hip and knee operations which are carried out each year in National Health Service (NHS) hospitals.

Private healthcare providers have also been interested in using the Oxford orthopaedic scores, including the OHS, to develop care pathways that achieve the best possible results for the patients. Nuffield Health (UK) is just one of our user community to obtain benefit from the OHS in this way.

Attributes

- a simple scoring and summing system provides an overall scale for assessing outcome of hip interventions
- the PRO is completed by the patient, independent of the clinical team/surgeon
- the PRO can be completed anywhere, can be delivered by post to patients' homes or deployed by various electronic platforms such as web or PDA. This makes follow-up of large study populations much more feasible (and cheaper) than conducting clinical assessments, requiring a return visit to the hospital.

Apply to use

The OHS 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

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39 translations available

Find out more!

The Oxford Knee Score (OKS)

Clinical Outcomes

The Oxford Knee Score (OKS) is a 12-item patient-reported PRO specifically designed and developed to assess function and pain after total knee replacement (TKR) surgery (arthroplasty). It is short, reproducible, valid and sensitive to clinically important changes.

Background

The OKS was designed to be completed by the patient thus minimising potential bias unwittingly introduced by surgeons when assessing the results themselves.
The PRO was designed and developed by researchers within Public Health and Primary Health Care at the University of Oxford in association with surgical colleagues at the Nuffield Orthopaedic Centre.

The PRO

The OKS is a patient self-completion PRO containing 12 questions on activities of daily living. The OKS has been developed and validated specifically to assess function and pain after TKR.

Attributes

- a simple scoring system provides an overall scale for assessing outcomes of knee interventions
- the PRO is completed by the patient, independent of the clinical team/surgeon
- the PRO can be completed anywhere, can be delivered by post to patients' homes or deployed by various electronic platforms such as web or PDA. This makes follow-up of large study populations much more feasible (and cheaper) than conducting clinical assessments, requiring a return visit to the hospital
- It eliminates interobserver error
- Users have reported extremely good response rates – 98% (Medalla 2009)
- In large scale studies the OKS has been ranked the best disease/site-specific PRO for assessing outcome of knee arthroplasty (Dunbar 2001)

Development

Similar to the situation with hip replacement, prior to the development of the OKS, only crude measures of surgical failure such as the need to perform revision surgery had been employed in the assessment of patient outcomes.

The development of the OKS was driven by the need to conduct more systematic and accurate monitoring of patient outcomes following TKR. As a relatively short instrument the OKS is particularly appropriate for use by older individuals who most often receive TKR.

Formats available:

- Paper
- Telephone administered version

Example study

The Oxford Knee Score and the Oxford Hip Score (OHS) have been adopted by the UK Department of Health (DoH) for the assessment of approximately 120,000 hip and knee operations which are carried out each year in National Health Service (NHS) hospitals.

Apply to use

The OKS 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

46 translations available

Find out more!

Oxford Knee Score – Activity and Participation Questionnaire (OKS-APQ)

Clinical Outcomes

Oxford Knee Score – Activity and Participation Questionnaire (OKS-APQ) is an 8-item, patient-reported outcome measure intended as a companion/adjunct to the Oxford Knee Score, for assessing higher levels of activity and (social) participation.

Background

OKS-APQ was developed by researchers within the Health Services Research unit, part of the Nuffield Department of Population Health, and the Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences (NDORMS) at the University of Oxford.

The PRO

It is a Patient Reported Outcome (PRO) Measure designed and validated to complement the Oxford Knee score as an additional scale. Where the OKS is essentially pain and disability-based, the new questionnaire incorporates important additional issues raised by relatively younger or more active patients. The OKS-APQ is a concise measure, with a single domain.

Development

Stage 1 – Item generation

Semi-structured, in-depth interviews were carried out with 26 patients, with osteoarthritis (OA), attending orthopaedic or pre-admission clinics at a regional centre, either under consideration for knee replacement, or already awaiting Total Knee replacement (TKR) or Unicompartmental Knee Replacement (UKR) within the next four weeks, or had undergone TKR or UKR between two and 24 months previously.

A set of preliminary questionnaire items were then discussed with an expert panel and refined to produce a draft questionnaire. The draft questionnaire was then piloted with new patients in clinics in three different formats (all with five category Likert scale), a brief cognitive interview then followed and an independent formal assessment of readability and translatability was also conducted resulting in a draft 17-item questionnaire.
alongside the OKS and unlike the latter, is not recommended to be used as a stand-alone instrument.

Stage 2 and 3 – Item reduction and scale generation; testing scale properties

A first postal study (n=73) was conducted using the 17 item questionnaire generated at stage one, along with the Oxford Knee score and the SF-36 generic health questionnaire (Mental Health Component Summary Score (MCS) and Physical Component Summary Score (PCS)). The resulting data was analysed to identify any issues with items and assess internal consistency (using Cronbach's alpha). The formal process of item reduction used Exploratory Factor Analysis (EFA), Confirmatory factor Analysis (CFA) and Rasch analysis. Analyses were revisited to confirm the validity of the measure across methods.

Construct validity of the OKS-APQ was examined by correlation with the OKS, SF-36 and Knee and Functional American Knee Society Scores (AKSS) results. There were nine items removed in total: four items because of the high celling effect, another four in order to have clear factor structure (that excludes any item) and one item with more that 10% missing data.

The final eight-item questionnaire seems acceptable to patients, as demonstrated by high response rates (effect size 4.16). It has a high level of internal consistency and no redundant items. The OKS-APQ is designed to be used alongside the OKS and unlike the latter, is not recommended to be used as a stand-alone instrument.

Scoring system

The OKS-APQ provides a single summed score which reflects the severity of problems that the respondent has with their knee. Details of the scoring system for the OKS-APQ can be downloaded in Dossier Extracts section.

Apply to use

The OKS 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:

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+44 (0) 1865 614480

6 translations available

Find out more!

The Oxford Shoulder Instability Score (OSIS)

Clinical Outcomes

The Oxford Shoulder Instability Score (OSIS) is a short, 12-item, condition-specific, patient reported outcome (PRO) measure developed and validated for measuring surgical and non-surgical therapeutic outcomes of patients presenting with unidirectional or multi-directional instability of the shoulder.

Background

The OKS was designed to be completed by the patient thus minimising potential bias unwittingly introduced by surgeons when assessing the results themselves.
The PRO was designed and developed by researchers within Public Health and Primary Health Care at the University of Oxford in association with surgical colleagues at the Nuffield Orthopaedic Centre.

The PRO

The OSIS is a patient self-completion PRO measure containing 12 questions on activities of daily living particularly relevant to patients exhibiting shoulder instability. The OSIS has been specifically designed to assess outcome of therapy (both surgical and non-surgical) by measuring activities of daily living and pain of patients exhibiting shoulder instability.

Attributes

- **Short**
  The OSIS is a 12 item uncomplicated questionnaire. It therefore benefits from high completion rates. The OSIS is easy to deploy across diverse healthcare applications.
- **Reliable**
  Published results (see development paper) on patient groups demonstrate the reproducibility and internal consistency of the score.
- **Valid**
  The OSIS has been shown to correlate well with existing related clinical and generic PRO measures.
- **Sensitive to change**
  Effect size for the OSIS is large and results (see development paper) clearly show it outperforms generic PROs, including those with a physical role dimension.
- **Practical**
  Easy to complete and can be given to the patient at clinic or sent by post.

Development

The OSIS was developed using a multi-stage process, consistent with industry best-practice methods. The OSIS joins a portfolio of well-regarded and widely used orthopaedic PRO measures created by Dr Jill Dawson at the Health Services Research Unit (HSRU) in association with colleagues at the Nuffield Department of Population Health and the Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences (NDORMS) at the University of Oxford.

The development of the OSIS was supported by world-leading clinicians at the NDORMS led by Professor Andrew Carr. Professor Carr was elected a fellow of the Academy of Medical Sciences in 2009 and is President elect of the British Elbow and Shoulder Surgery Society.

The items in the OSIS were derived from exploratory interviews rather than from clinical assumptions. Draft versions were tested on patients and the final content only agreed when patients understood it and felt no important items had been omitted. Subsequent testing of the OSIS was conducted on 92 patients exhibiting problems related to instability of the shoulder. Test results from the study of the 92 patients show the OSIS to be reliable, valid and sensitive to change.

Apply to use

The OSIS 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

10 translations available

Find out more!

The Oxford Shoulder Score (OSS)

Clinical Outcomes

The Oxford Shoulder Score (OSS) is a 12-item patient-reported PRO specifically designed and developed for assessing outcomes of shoulder surgery e.g. for assessing the impact on patients' quality of life of degenerative conditions such as arthritis and rotator cuff problems.

Background

The development of the OSS was driven by demands for a suitable PRO by orthopaedic surgeons who wished to measure the outcomes of their treatments from the patient's perspective.

The OSS was designed and developed by researchers (within the Health Services Research unit, part of the Nuffield Department of Population Health at the University of Oxford) who also created the Oxford Hip and Knee scores, which are used for assessment of all NHS hip and knee surgeries (approximately 120,000) since April 2009. Designed and developed in association with surgical colleagues at the Nuffield Orthopaedic Centre the OSS has been tested in a surgical context with patients and shown to be reliable, valid and responsive.

First published in 1996, the OSS has gradually been adopted as an outcome measure and is now widely used in clinical studies.

The PRO

The Oxford Shoulder Score is a unidimensional score comprising 12 questions. A single score is derived from the PRO. Substantial evidence from clinical studies shows that the PRO has high internal consistency and is a valid and reliable measure of patient well-being.

Attributes

- the only condition-specific PRO designed and developed for use in assessing surgery intervention of the shoulder;
- has undergone rigorous testing for validity, reliability and sensitivity to change and has been shown to be a robust tool for assessing the outcome of shoulder surgery;
- can be employed in surveys or clinical trials for shoulder surgery patient groups;
- has been shown to be highly responsive to interventions and can be used as an indicator for recovery and general improvement in quality of life following shoulder surgery;
- brief and easy to complete resulting in good return rates;
- the PRO can be completed anywhere and delivered by post/electronically, making follow-up of large numbers of patients much more feasible (and cheaper) than conducting clinical assessments;
- easy to interpret scores.

Formats available:

- Paper
- Telephone administered version

Apply to use

The OSS 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

28 translations available

Find out more!

OXFORD Ankle Foot Questionnaire for Children (OxAFQ-C)

The Oxford Ankle Foot Questionnaire for Children (OxAFQ-C)

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Clinical Outcomes

The Oxford Ankle Foot Questionnaire for Children (OxAFQ-C) is a child – or parent (proxy)-reported self-report health status PRO.

Background

The The Oxford Ankle Foot Questionnaire for Children (OxAFQ-C) is used to measure subjective well-being for child patients (aged 5-16) affected by foot and ankle conditions using issues that are considered important to children.

Typical clinical assessments fail to capture the child patient's perspective and may not accurately reflect how children function in their usual environments. The OxAFQ-C was therefore designed to supplement clinical assessments to evaluate the effectiveness of interventions for ankle/foot problems in children.

The PRO

The The Oxford Ankle Foot Questionnaire for Children (OxAFQ-C) is used to measure subjective well-being for child patients (aged 5-16) affected by foot and ankle conditions using issues that are considered important to children.

Typical clinical assessments fail to capture the child patient's perspective and may not accurately reflect how children function in their usual environments. The

Attributes

- The OxAFQ-C is rapidly gaining acceptance as the PRO of choice for assessing the impact of ankle/foot conditions in children for the following reasons:
- It is the only PRO available assessing the impact of ankle foot issues on children from both the child and parent/-caregivers perspective;
- The OxAFQ-C has broad utility both in routine clinical settings or applied research comparing different treatment programmes used in paediatric orthopaedics, trauma and rheumatology;
- A short (15-item) questionnaire that has proven to be easy to complete and returns high completion rates; Has been proven to be a valid and reliable (Morris et al 2008, see reference below) as well as being responsive and longitudinally valid (Morris et al 2009).

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 OxAFQ-C 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:

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13 translations available

Find out more!

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.

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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:

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26 translations available

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.

Formats available:
- Paper - Telephone administered version

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:

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

The PDQ 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:

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87 translations available

Find out more!

Parkinson's Disease Questionnaire – Carers (PDQ-Carer)

Clinical Outcomes

The Parkinson's Disease Questionnaire-Carer (PDQ-Carer) is the first well documented, simple scoring measure of quality of life among this population.

Background

Carers can be an important source of help and support to people with long term conditions, such as Parkinson's disease (PD). Carers for people with PD can face numerous responsibilities arising from the need to provide support and assistance to a person they care for. This is particularly important for those caring for a person with a progressively disabling disease which can have direct implications upon their quality of life.

The Parkinson's Disease Questionnaire-Carer (PDQ-Carer) is the first well documented, simple scoring measure of quality of life among this population. Consistent with best practice, the developers of the PDQ-Carer have incorporated the views of carers of people with PD throughout the PROs development.

The PDQ-Carer was developed by researchers in the University of Oxford who are responsible for the development of the Parkinson's Disease Questionnaire-39 (PDQ-39) (also available through our clinical outcomes team). The PDQ-39 is the most widely

Attributes

Valid
The PDQ- Carer demonstrates good content and construct validity.

Reliable
The PDQ- Carer exhibits good internal consistency.

Acceptable
Pre-testing and high completion rates suggest that the PDQ-Carer is easy to complete and acceptable within the test population.

Easy to administer
The PDQ-Carer is a self-administered, paper based PRO. It is both short and easy to score.

Can be used with the developers' corresponding patient questionnaire (the PDQ-39)
The PDQ-Carer can be used in conjunction with the established PDQ-39 to allow test administers to correlate quality of life scores of a person with PD and their respective carer.

The PRO

There are 29 items in the PDQ-Carer, representing four discrete scales:

- Social and personal activities (12 items)
- Anxiety and depression (6 items)
- Self-care (5 items)
- Stress (6 items)

The PRO asks about the influence of caring on specific areas of life over the past four weeks. Respondents are asked to select one of five response options: Never/Occasionally/Sometimes/Often/Always.

Scoring system

The PDQ-Carer benefits from a simple scoring system. The raw score of each scale can be calculated and converted to a 0-100 metric where 0=no problem at all and 100=worst or maximum level of problem. The sum of the scale scores can provide a single figure used to assess the overall quality of life of the individual questioned.

Apply to use

The PDQ0-C 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:

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+44 (0) 1865 614480

12 translations available

Find out more!

Parkinson's Disease Questionnaire - Exercise (PDQ-Exercise)

Clinical Outcomes

The Parkinson's Disease Questionnaire – Exercise (PDQ-Exercise) is the first Exercise-Specific Parkinson's Disease Questionnaire.

Background

Treatment for Parkinson's disease (PD) has traditionally depended largely on pharmacological intervention. However, exercise is now also recognized as a significant and key component in the management of the condition.

Despite the increasing prominence of exercise therapy in PD management, no self-report, Parkinson's-specific measure of exercise existed, that was solely aimed at measuring these elements with adequate sensitivity. The PDQ-Exercise may help identify specific interventions and/or PD population groups for which exercise interventions will have the highest impact, levels of adherence, and compliance.

Development

The PDQ-Exercise was developed in compliance with current best practice, guidance by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA), which places People with Parkinson's (PwP) at the heart of the development process.

The study leading to the creation of the PDQ-Exercise comprises three phases: item generation interviews (20 PwP), pretesting (14 PwP), and a validation survey (398 PwP). Item generation interviews were face-to-face and qualitative to identify concepts of relevance that did not previously exist in the PDQ 39.

The reliability of the PDQ-Exercise is demonstrated by ITCs (item-total correlations) that confirm individual item scores relate to the overall score. The validity of the new measure is established through the assessment of correlations with the PDQ-8 and the three domains of the Oxford Participation & Activities Questionnaire (Ox-PAQ).

Additional psychometric properties, such as test–re-test reliability and sensitivity to change (thus allowing its use over time), are currently being assessed and will be reported in due course.

The PRO

The PDQ-Exercise is a 7-item short questionnaire that can be administered as a stand-alone measure of quality of life in studies and clinical trials centred around exercise therapy, or as a complement to the Parkinson's Disease Questionnaire (PDQ).

Scoring system

The PDQ-Exercise is calculated as a single domain scale ranging from 0-100. Higher scores indicate greater problems with exercise related issues.

Complementary PRO Measures

- The Parkinson's Disease Questionnaire (PDQ-39)
- The PDQ-8, the short-form version of the PDQ-39
- The Oxford Participation and Activities Questionnaire (Ox-PAQ)

Users can cover quality of life in wider scope studies by utilising an appropriate combination of these measures although specific correlation data is not yet available.

Apply to use

The PDQ-Exercise 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:

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+44 (0) 1865 614480

Find out more!

Postoperative Quality of Recovery Scale (PostopQRS™)

Clinical Outcomes

The Post-operative Quality of Recovery Scale (PostopQRS™) is a quick and easy-to-use web-based digital clinical outcomes assessment (eCOA) that measures the quality of recovery of patients undergoing surgery and/or anaesthesia

Background

PostopQRS™ is clinician lead and provides objective assessment of post-operative recovery analysing the core domains of recovery (physiologic, nociceptive, functional, cognitive, and emotional recovery).

PostopQRS™ is a digital measurement tool, that is CE Marked as a Class 1 Medical Device within the UK and Europe used to assess multiple domains of post-operative recovery over time. The PostopQRS™ can be administered as a pen and paper completion questionnaire too.

The quality of recovery following surgery and anaesthesia is of vital importance to improving patient outcomes and clinical practice. "What happens in the operating room may influence recovery well beyond hospital discharge".

Key Features

- The PostopQRS™ provides objective assessment of post-operative recovery
- Physiologic, nociceptive, functional, cognitive, emotional recovery domains can be assessed as well as overall patient perspective for a comprehensive assessment instrument
- Assessment of the effects of surgery from both clinician and patient perspectives, the PostopQRS™ is a powerful combination of PRO, ClinRo and PerfO delivering a comprehensive measure of recovery
- Repeated measures (n=4 recommended) allow for assessment over time, from immediate recovery to long-term follow up
- The PostopQRS™ can be used as an early warning system to failing recovery
- The PostopQRS™ is procedure agnostic and can be employed to assess recovery for elective, day, or ambulatory surgeries
- It can be completed in 5-6 minutes by adults and children over the age of 6.

Administration

The PostopQRS™ is available via an off the shelf platform on the PostopQRS™ website, where users can sample up to 5 free administrations.

Although available in electronic format, the PostopQRS™ can legitimately be administered in paper-based format and results transcribed to the PostopQRS™ website for scoring and analysis purposes.

Who is using the PostopQRS™?

The international PostopQRS™ userbase is made up of 350+ registered users in a variety of applications spread across the healthcare sector, but includes:-

- Hospital clinicians and/or managers seeking to improve patient outcomes, optimise pathways, improve discharge data and help reduce readmissions.
- Health outcome registry managers who are seeking a standardised measure to gather evidence of local, regional, national, or international surgical recovery outcomes.
- Trial managers in (or eCOA service providers serving the needs of) the medical device or pharmaceutical sectors seeking to objectively evaluate and compare interventions over time.

Apply to use

The PostopQRS™ is managed 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

12 translations available

Find out more!

Patient Reported Experiences and Outcomes of Safety in Primary Care (PREOS-PC)

Clinical Outcomes

The PREOS-PC is a patient / service user self-complete questionnaire which is designed to comprehensively measure experiences and outcomes related to patient safety in the primary care/ambulatory setting.

Background

Current tools measuring patient safety rely on information provided by healthcare providers. However, evidence suggests that patients can recognise problems in health care delivery that are not identified by current systems of health care monitoring.

Developed with the support of the National Institute for Health Research (NIHR), the PREOS-PC is designed to be a comprehensive collection of information about the patient experience and patient safety problems within primary care.

The PREOS-PC consists of three versions; a short form, a compact form, and a comprehensive version, all of which can be used independently to assess five domains of patient safety in primary care in unique ways. It was developed by experts assisted by patient input and is valid for use in primary care.

- The comprehensive form provides a comprehensive overview of patient safety while offering the best metric properties, whether for research or for the routine in-depth evaluation of service delivery.

- The compact form offers a balance of both high psychometric standards and reduced administrative burden, facilitating its implementation and use in actual practice.

- The PREOS-PC Screen offers a succinct summary of patient perception of safety that can be embedded in broader audits and evaluations of service delivery, ensuring adequate coverage of key domains.

The measure

A conceptual framework was developed for the PREOS-PC based on three necessary elements for patient safety events:

1. Patient interaction with the health care system, including self-management
2. Standards of care
3. Actual or potential harm to patients

The PREOS-PC consists of 5 domains:

· Practice Activation (the degree to which practices are perceived to be engaging in promoting safety)

· Patient Activation (the degree to which the patient engaged in promoting safety)

· Patients' experiences of safety problems Impact on Health

· Patient safety outcomes (harm)

· General perceptions of safety

The measure has been shown to have good content and face validity and be acceptable to patients.

What the meausre provides

· A comprehensive collection of information about patients' experiences and outcomes of patient safety problems in primary care.

· Discrimination between different levels of patient safety between practices and over time.

· Independent usage of different versions, depending on desired degree of granularity.

Apply to use

The PREOS-PC 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 PREOS-PC please get in touch with the Clinical Outcomes team via:

healthoutcomes@innovation.ox.ac.uk

+44 (0) 1865 614417

3 translations available

Find out more!

ReQoL™ Recovering Quality of Life

The University Of Sheffield.

Recovering Quality of Life (ReQoL) Questionnaire

OXFORD UNIVERSITY INNOVATION

UNIVERSITY OF OXFORD

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

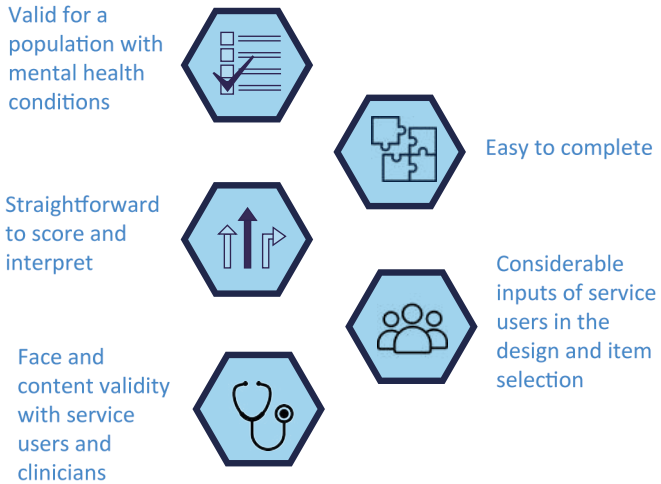
ReQoL is a brief outcome measure focusing on the process of recovery for users of mental health services. Developed by a team at The University of Sheffield to capture the concerns of service users on their quality of life. This work was commissioned and funded by the Department of Health Policy Research 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

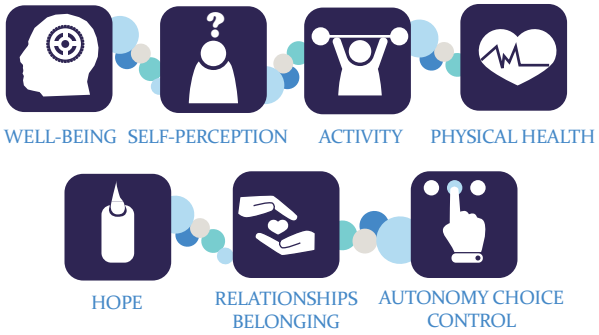
Comprehensive psychometric testing has shown that the ReQoL is:



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:



Formats available:

- Paper - Telephone administered version

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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New

Utility Index version for calculation of QALYs now available!

23 translations available

Find out more!

The Bluebelle Wound Healing Questionnaire (WHQ)

Bluebelle
Wound Healing Questionnaire

Clinical Outcomes

The Bluebelle WHQ is an 18 item questionnaire for the assessment of surgical site infection (SSI) in closed primary wounds

Background

The Bluebelle WHQ is a single measure designed for completion by patients (using the PRO version) or healthcare professionals (using the ClinRO version) during a period of up to 30 days after discharge from hospital. The questionnaire includes items to assess signs, symptoms and wound care interventions indicative of SSI. Response categories include an ordinal scale to capture symptom severity. Development of the measure involved patients and professionals using robust methodology.

The questionnaire is available in two different versions.

- **Patient reported (PRO)** version of the Bluebelle. To be completed by the patient themselves after leaving hospital following surgery.
- **Clinician reported (ClinRO)** version of the Bluebelle. To be completed by any healthcare professional involved in wound assessment.

The Bluebelle study was funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme (project number 12/200/04).

Key Features

Acceptable - Pre-testing and high completion rates suggest that the Bluebelle WHQ is easy to complete and acceptable within test population.

Good Scale Structure - Exploratory factor analyses examined the underlying structure and constructs of the questionnaire, resulting in good content and construct validity.

Reliable - Test–retest reliability was assessed by comparing self-assessment responses to the WHQ completed twice over a period of anticipated stable health.

Valid - Criterion validity was examined against the reference SSI diagnosis to demonstrate how well the WHQ performed in discriminating between individuals with and those without SSI.

Scoring

The WHQ consists of a single scale. An overall score is calculated by simply summing the scores for each item. When summed, possible overall scores range from 0 to 41 with a lower score representing a better wound healing outcome. There are no pre-defined recommendations from the developers for dealing with missing values, with the exception of an optional component for Item 6 (Item 6b).

Further Research

Research into the further application and validation of the WHQ in other types of wound and surgical specialties is underway. Cut-off scores for SSI diagnosis will be explored further.

In addition, members of the research group are exploring the feasibility of collecting digital images of the wound taken by patients as a tool to use in conjunction with the WHQ for improving remote and blinded SSI assessment.

Apply to use

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2 translations available

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