# Dementias Platform UK

Medical Research Council

**Annual Report**

July 2015 - June 2016

# A world-leading resource for person-focused dementias research

Dementias Platform UK (DPUK), funded by the Medical Research Council, is a multi-million pound public-private partnership aiming to accelerate progress in, and open up, dementias research. It began in June 2014 and was officially launched the following October. The project is directed by Professor John Gallacher from the University of Oxford, supported by an Executive Team of investigators.

DPUK's academic partners are the University of Cambridge, Cardiff University, the University of Edinburgh, Imperial College London, the University of Manchester, the MRC Biostatistics Unit at the University of Cambridge, Newcastle University, the University of Oxford, University College London (UCL), including the UCL-based MRC Unit for Lifelong Health and Ageing, and Swansea University. The Clinical Research Infrastructure Award links DPUK with the University of Bristol. Industry partners from within the pharmaceutical industry are GSK, Janssen Research & Development, AstraZeneca-MedImmune, Ixico, SomaLogic and Araclon.

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MRC Biostatistics Unit
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The University of Edinburgh
Swansea University Prifysgol Abertawe
AstraZeneca



# Contents

*Professor John Gallacher*

# Foreword

DPUK is a response to the global need to understand more fully the causes of dementias, and the need for a new generation of early phase dementia trials. It supports these goals by bringing together multiple cohort studies and making these more accessible to researchers. This enables science to be done more quickly and reliably, which in turn will bring about more accurate bases for trials and evidence for identifying effective treatments.

This report provides an overview of project activity as the MRC Dementias Platform UK (DPUK) completes its second year. It reviews the year to July 2016, through insights into the research funded by the Medical Research Council and facilitated by DPUK. The people of the project are represented, through written reports and reflective articles. Finally, it sets out next steps for DPUK.

There have been several key outcomes this year. Our relationships with cohorts through their Principal Investigators (PIs) have strengthened; the DPUK networks for PET-MR imaging, induced pluripotent stem cell research and informatics are up and running across the UK; and DPUK has attracted considerable further funding.

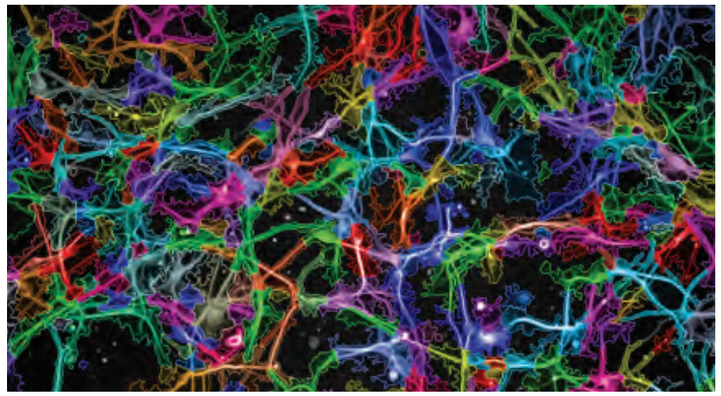
Should this report prompt any questions or suggestions for you, please contact me: it is through our collaborative work that we will deliver ground-breaking outcomes for dementias.

**Professor John Gallacher**
PhD AFBPsS CPsychol FFPH
Director, MRC Dementias Platform UK



# Five year vision

Our vision is to provide an integrated research environment enabling a new generation of highly-targeted and highly-informative clinical trials linking more closely cellular and molecular changes to patient selection and response. Within five years we will establish world-leading data sharing facilities, world-leading research networks for imaging, stem cells and informatics, and systematic experimental medicine programmes focusing on synaptic health, innate and adaptive immunity and vascular disease mechanisms.



*iPSC neuronal network, visualised using the Opera Phenix high-throughput cell screening system, purchased through the MRC Clinical Research Infrastructure award*

# Platform objectives

- To create an integrated environment for dementias research, in which the scientific community can generate and access data to aid understanding of the dementias.
- To develop a single-point data access portal for analysing cohort data.
- To establish an imaging network across the UK, with state of the art MRI-PET capabilities, coordinated research activity and a common data repository.
- To establish an induced pluripotent stem cell network across the UK, enabling the development of new technologies, strategic preservation of primary cells, and coordinated research programmes.
- To establish an informatics network across the UK supporting the collection and integration of high and low dimensional data, device-generated data, and electronic health records.
- To integrate data from multiple cohorts to enable rapid and extensive evidence synthesis.
- To repurpose strategically selected cohorts for dementia mechanisms discovery and trials readiness.
- To develop an integrated and systematic programme of experimental medicine, in partnership with industry, focusing on the early detection of decline and treatment of dementias.
- To demonstrate the value of collaborative working and leverage further resources for dementia research.

# Introduction

DPUK's goal is to improve the global understanding of the causes of dementia by enabling a new generation of early phase dementia trials. It owes its success to a range of factors: the UK's strong position of high-level technologies and portfolio of rigorously-maintained population studies; world-leading scientists and pharmaceutical companies; and the generous support of funding and encouragement from the MRC which has created this highly collaborative – and ground-breaking – public-private partnership.

DPUK is funded by the MRC in partnership with industry. It has received a core award over five years of £12m from the MRC, with a further £4m contribution from industry partners. In addition it has been awarded £36m by the MRC to establish three high-technology research networks: a molecular and structural imaging network across seven sites, an induced pluripotent stem cell network across six sites and an informatics network across five sites. These are now all up and running (see diagram opposite).

DPUK has been instrumental in dementia researchers from across the country submitting highly competitive grant proposals to a range of funders. Over the last 12 months, three grants totalling £9m have been awarded by the MRC Neurosciences and Mental Health Board and the National Institute for Health Research (NIHR), alongside a MRC Clinical Fellowship and a grant from Alzheimer's Research UK. Other grants applications are in process.

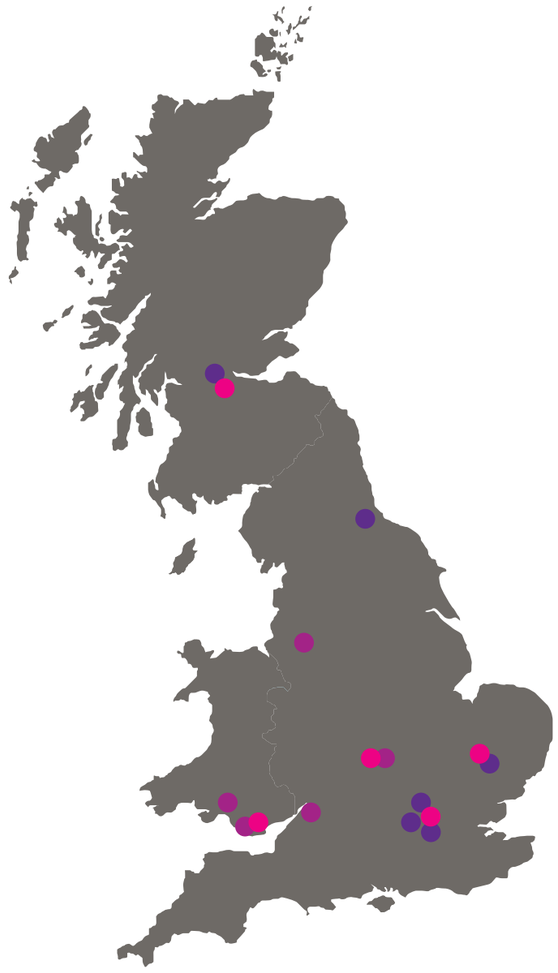
DPUK's greatest strength is its collaborative ethos, enabling the sharing of ideas, data, and best practice across the dementia research community. From this, we can develop an integrated research environment which really does work for everyone. Over the past year we have continued to develop this ethos by welcoming new academic partners (Manchester and the MRC Biostatistics Unit) to the platform.

## DPUK technology network

Seven centre Imaging Network
Six centre Stem Cell (iPSC) Network
Five centre Informatics Network

***DPUK technology networks national coverage***

- *Imaging Network*
- *iPSC Network*
- *Informatics Network*





# DPUK in translational space

DPUK has been created in anticipation of an increased need for trials in the early stages of dementia. It provides a context for a new generation of highly-targeted (risk-stratum specific), highly-informative (mechanism specific) trials. To achieve this, an enabling infrastructure has been established with three core utilities:

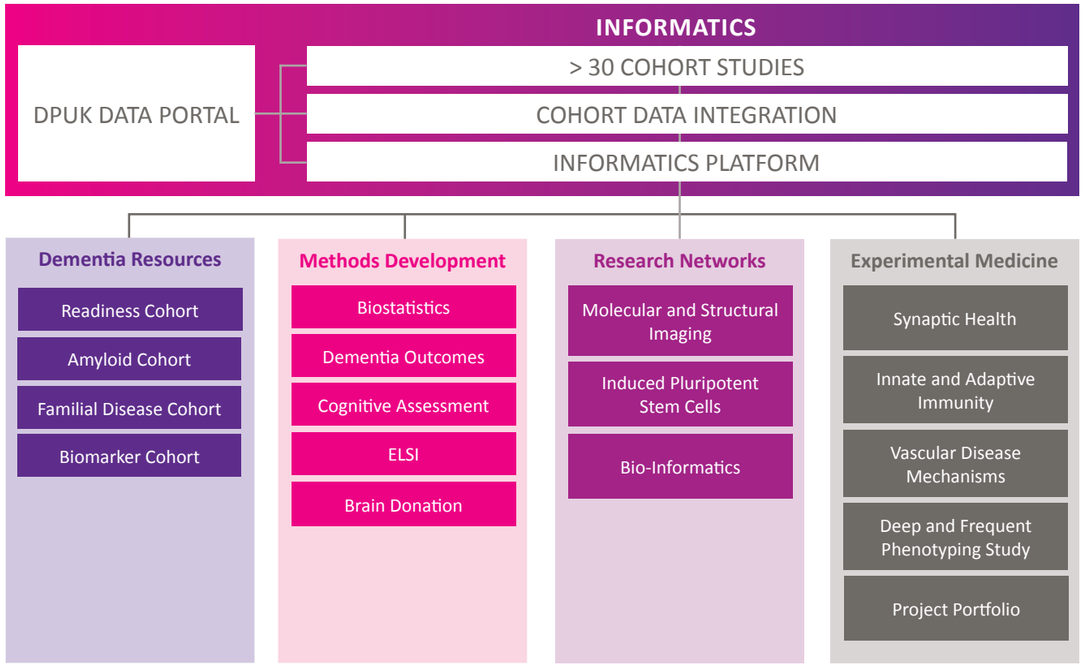
- Rapid data access enables triangulation between multiple independent datasets for in-silico experiments and other analyses
- Identification of highly-characterised participants enables recruitment to highly-targeted clinical studies including early phase trials
- Technology capacity building enables multi-centre studies using molecular and structural imaging, stem-cell, and bioinformatics networks.

Rapid data access is achieved through our data portal, which is designed to allow remote access to data from UK and international cohorts. All data analyses are conducted within the secure informatics environment and data are not downloadable. Over the past year the portal build has been completed and the necessary legal agreements have been drafted. We will begin uploading cohort data in Q3-4 2016.

The portal enables the identification of highly-characterised cohort participants for recruitment to clinical studies. This is breaking new ground and care is required to develop best practice that positively engages cohort participants and delivers efficient recruitment without compromising the scientific value of the cohort. Over the past year, qualitative work has been conducted to identify best practice, and clinical studies (European Prevention of Alzheimer's Dementia Consortium and the Deep and Frequent Phenotyping Study) have been identified as initial tests of the recruitment pipeline.

In anticipation of increased interest in, and funding for, dementia research, our technology networks have increased UK capacity to conduct multi-centre studies and generate internationally-competitive, dementia-focused research programmes. Through the sharing of best practice and the development of niche expertise, these networks aim to become global centres of excellence. During this second year a complex procurement for the networks has been completed and scientific activity begun. To pump-prime network activity we have a modest experimental medicine programme which has continued to develop during this second year.

These core enabling utilities allow DPUK to inhabit an unusual space in the dementia translational pipeline, forming a bridge between bio-molecular discovery science and population-based trials. We continue to approach this space flexibly, looking for opportunities to collaborate with other initiatives in and around this space to increase scientific opportunity generally.




*The DPUK research infrastructure: Linking cellular and molecular changes to patient selection and response*

# Informatics: The Data Portal

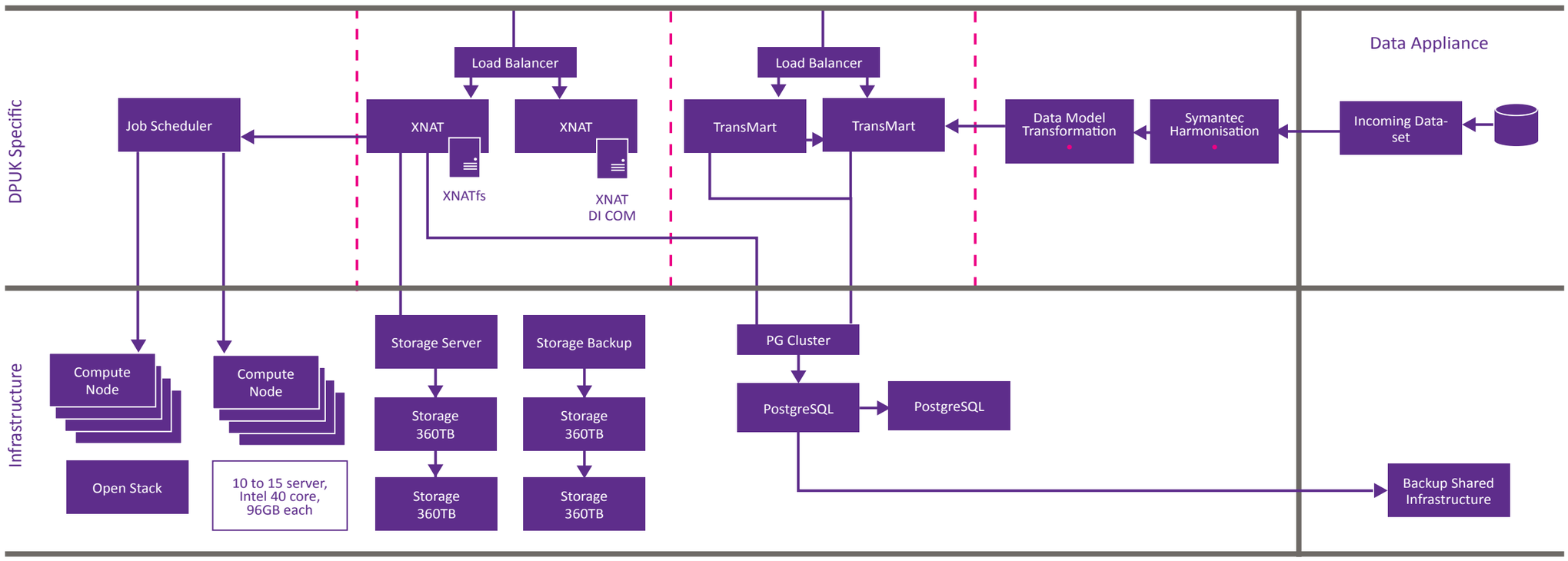
***The DPUK Data Portal is the engine driving DPUK data storage and analysis. Using UKSeRP technology developed by the Farr Institute, the portal provides a safe-haven for sensitive data, enabling both storage and analysis within the same secure environment.***

Data may not be downloaded from the portal by researchers. Over the past year, portal build has been completed and the data transfer and data access legal agreements are being finalised.

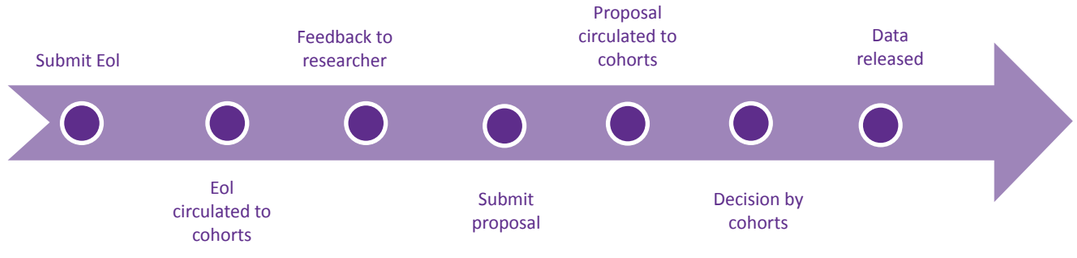
Improving portal utility is an ongoing process as we seek to make data access within our secure environment as convenient as possible. Currently, additional metadata tools which have been developed by the IMI-funded EMIF project are being added to the portal. These tools enable more detailed interrogation of cohort data to identify variables and participants that are relevant for specific analyses.

Key to improving UK data access are standard and convenient data access procedures. In the absence of this utility, UK cohorts have of necessity developed bespoke access procedures, which vary considerably. This variation adds unnecessary complexity to the UK cohort data access landscape. It also means that the process of identifying best practice and its adoption as a standard is gradual, requiring the differing needs and concerns of cohorts to be addressed.

DPUK is using its data portal as a data access hub that can be used as a vehicle for developing common data access practices across cohorts. The model is to provide a one-stop-shop for scientists to 1) access metadata to identify data relevant to the research question;
2) be a single point of contact for multiple cohorts to obtain approval for data access;
3) complete the legal and technical requirements for data release. The process has been designed to reduce the risk of application failure by introducing feedback based on an expression of interest from the cohorts to the applicant prior to a proposal being made (see figure: the DPUK data access pipeline).This model has been broadly welcomed, as the potential advantage of a single process is clear. A major challenge is integrating the bespoke access process of each cohort with those of DPUK, avoiding two processes running in parallel. It is anticipated that integration will be gradual. Once the DPUK process is established and demonstrably reduces the transaction costs of data access for all stakeholders, it is anticipated that integration will accelerate.




*The DPUK Data Portal sits on a bespoke version of UK Secure eResearch Platform infrastructure. This includes image storage, a high-performance computing cluster, TranSMART and EMIF tools.*




*The DPUK data access pipeline*

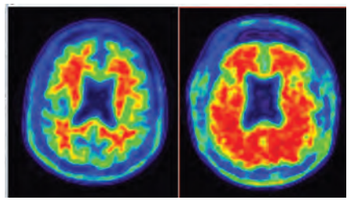
# Dementias resources

## Trials readiness cohort

The work with UK Biobank to establish a cohort of 100,000 adults with brain imaging, genotyping and cognitive phenotyping continues, with DPUK providing an enhanced cognitive battery for the imaging assessment, and a brain-donation protocol. This past year has seen the completion of the enhanced cognitive assessment battery and its introduction to the UK Biobank imaging assessment. Recruitment to this cohort is running to time and budget, with 7,000 imaged by July 2016. DPUK is funded to provide repeat brain imaging at two years for 10,000 UK Biobank participants. Recent pilot work by UK Biobank has shown that around 80% of baseline imaging participants are willing to return for repeat imaging. Although the actual response rate is likely to be lower, it remains encouraging.

## Amyloid marker discovery cohort

Deposition of β-amyloid is thought to be a very early feature of Alzheimer's disease (AD). To identify non-invasive markers of β-amyloid, 500 members of the MRC National Survey of Health and Development are currently taking part in a large study (Insight 46) which also includes DPUK Work Package 4. The Insight 46 study participants are undergoing detailed cognitive assessments, amyloid PET/MR imaging and fluid (blood and urine) biosampling. Recruitment is on course and, as of September 2016, 209 cohort members have been assessed and imaged. Early analysis is underway, with the aim that once recruitment is completed, the structural MRI scans and biofluids can be used to develop new methods of detecting individuals at risk of developing AD.



*Amyloid negative (left) and positive (right) PET scans from the Insight 46 study*

## Familial disease cohort

The familial disease cohort aims to provide unique biomarker validation of disease-specific and disease-common biomarkers. By comparing markers from different diseases (ie FAD, FTD and HD), the group hopes to identify common and unique mechanisms associated with these conditions. Over the last year, for the purposes of DPUK, recruitment has been extended to a number of studies, but with a focus on the tau imaging study because of its direct relevance to Alzheimer's disease. The group is currently undertaking a pilot of 24 tau mutation carriers, examining tau pathology using the PET ligand AV1451. This project is underway, with 17 individuals scanned (ten familial FTD, seven familial AD). Through DPUK funding, as an extension to the above, up to ten subjects with familial FTD will receive a follow-up [18F] T807 PET scan. The group recently received all approvals and the first follow-up scan is planned for September 2016.

## Biomarker discovery cohort

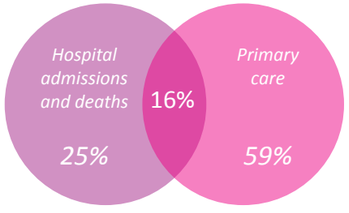
This work package will create a core molecular marker resource, providing opportunity for definitive replication of biomarker data generated in other cohorts as well as discovery of complex biomarker signatures. This resource will be of value internationally. An expert group will conduct extensive high-dimensionality molecular analyses on risk-stratified samples drawn from 1,500 DPUK cohort participants, to contribute to ongoing molecular biomarker studies. Starting early in 2017, the group will be focusing on genomic stratification. In contrast to most existing large biomarker studies, which are predicated on diagnostic categories, this group will use a variety of DPUK cohorts to stratify on the basis of genomics in three categories: familial dementias; rare variants of late onset disease; and polygenic risk score. Samples from 1,500 DPUK participants will be processed.



# Methods development

## Outcome adjudication

Identifying cases of dementia (and related neurodegenerative conditions) through routinely-collected linked healthcare data is a feasible way to ascertain dementia at scale in a wide range of population-based prospective studies. Progress to date includes three systematic reviews (one submitted and two being prepared for submission for publication) on the accuracy of routinely-collected healthcare data for identifying dementias, Parkinson's disease and motor neurone disease.
A validation study of dementia cases identified through linked healthcare data sources in Edinburgh-based UK Biobank participants provided interesting preliminary results showing the value and importance of achieving linkage to primary care data. There has also been a successful collaboration with researchers from the Whitehall II cohort, investigating the accuracy and yield of routinely-collected data and intermittent cognitive testing for identification of dementia cases.




*Venn diagram summarising the distribution of sources of dementia cases in UK Biobank routinely-collected data (101 dementia cases occurring in a subset of 27,000 UK Biobank participants with data from hospital admissions, death registers and primary care records)*

## Cognitive assessment at scale

It is important to find out why some people's cognitive functions age better than others'. Very large population-based studies of ageing bring the advantage of numbers, but require relatively brief cognitive assessments because participant time is precious. This group has developed an enhanced cognitive assessment battery for UK Biobank which has been implemented at the imaging clinic. It includes tests that are usually sensitive to age-related cognitive decline, and a test that estimates people's peak prior cognitive ability. Ongoing research is modelling UK Biobank cognitive assessment data, alongside genetic and other phenotypic data, to predict complex diseases and understand their associations with cognitive functions and education. Among current plans are an examination of the psychometric properties of the cognitive tests in UK Biobank, and an investigation of the cognitive data access process via the DPUK data portal.

## Ethical, legal and social issues

Developing a nationwide data-sharing collaboration to make experimental medicines research available to existing studies raises a range of ethical, legal and social issues. Work Package 12 has conducted a four-phase, in-depth qualitative study to examine these issues across the collaborating cohorts. Working with both research teams and research participants, this group has recognised the diverse perspectives, expectations and motivations of different stakeholders involved in research, to support ethically and socially robust innovation. The work package is now working to disseminate these findings, and collaborating closely with cohort participants to ensure their views are clearly represented in the future direction of dementias research in the UK.

## Brain donation

Working with large numbers of rigorously-maintained cohorts - large numbers of individuals carefully studied, with data recorded over a long period of time - provides an unprecedented opportunity for collecting well-characterised brains for research. The past year has focused on developing closer relationships with the UK Brain Banking Network (UKBBN) and completing a flexible consent procedure that enables selective collection of brains according to scientific purpose. The consent procedure is now ready for piloting in UK Biobank. Discussions with UKBBN are ongoing to develop a pilot scheme by which we can test the capacity of UKBBN to collect brains from DPUK cohorts.

## Genetics

To leverage the wealth of phenotypic and genetic data available in the DPUK cohort, statistical analyses have been developed. This includes publication of a polygenic risk score for Alzheimer's disease (Escott-Price et al, 'Common polygenic variation enhances risk prediction for Alzheimer's disease', Brain, 2015). Further to this, the group has shown that the polygenic score method captures the majority of all common genetic risk for Alzheimer's disease, making it a very valuable statistical technique (Escott-Price et al., 'Polygenic score prediction captures nearly all common genetic risk for Alzheimer's disease', Neurobiology of Aging, 2016).

## Biostatistics

The team is in the process of analysing cohort data, beginning by applying several novel variable selection methods to the CFAS genetic and baseline disease state or cognitive function scores to identify SNPs related to outcome. Results obtained from these methods may be pooled across to obtain robust results. Specific methods might include LASSO, elastic net, stability selection (penalised approaches), evolutionary stochastic search variable selection (ESS) using R package R2GUESS, non-local prior Bayesian variable selection using R package mombf and Bayesian variable selection for binary outcomes, using R package R2BGLiMS (Bayesian approaches). These are all multivariate approaches that model the joint effects of SNPs on outcome, with sparsity enforced through use of priors or penalties. We will then further consider using ESS to do joint modelling of more than one phenotype. We will then extend our work to consider risk stratification of individuals. A joint clustering and regression approach (profile regression, using R package PReMiuM) will be used to cluster individuals into groups that are associated with the outcome. We will finally validate our model using other independent DPUK cohort datasets that have the relevant information.

# Research networks

## IMAGING NETWORK

**Network Lead**
**Professor Paul Matthews, Imperial College London, Chair**

**Co-chairs**
Franklin Aigbirho, University of Cambridge
Nick Fox, University College London

**MRI-PET procurement**
Geoff Parker, University of Manchester. Edwin Van Beek, University of Edinburgh

**Radiotracer access & development**
Jan Passchier, Imanova/ Imperial College London. Franklin Aigbirho, University of Cambridge

**Multi-centre clinical operations**
Karl Herholz, University of Manchester. John-Paul Taylor, Newcastle University

**Harmonised analysis and QC pipeline implementation**
Roger Gunn, Imperial College London. Tim Fryer, University of Cambridge

**Informatics infrastructure**
Clare Mackay, University of Oxford. Sebastien Ourselin, University College London

***The DPUK Imaging Network has made considerable progress over the last year. A major task was to complete the procurement and installation of five new MRI-PET facilities focused on dementia research across the UK.***

State-of-the-art scanners now have been installed in Edinburgh, Newcastle, Manchester, Cambridge and Imperial College/Imanova. Along with the previously established centres at King's College and University College London, the UK now has a coordinated network of seven sites strategically positioned, north to south, which are committed to coordinated development and joint working.

Important steps towards the latter have been taken. Part of the resourcing from the MRC Capital Infrastructure Fund enabling the purchase of new scanners has been committed to the enhancement of radiochemistry resources at Imperial/ Imanova to make it possible for GMP radiotracers to be delivered outside of the Hammersmith Hospital Facility. Research agreements with the instrument manufacturers recognise the DPUK centres as international luminary sites and are facilitating work between them.
An informatics network based on use of the open access image management platform, XNAT, has been set up that involves all of the MRI-PET and the DPUK-associated 7T Network sites (MacKay, PI). An MRC Partnership award (Herholz, PI) now links all of the centres for MRI-PET operations harmonisation and training. An ARUK Network Award (Thomas, PI) will support development of a harmonised MRI acquisition protocol and its quality control. Planning for the 2017 initiation of the Deep and Frequent Phenotyping Study (Lovestone, PI), which involves linking intensive MRI and PET studies to a broad range of laboratory and clinical testing on subjects at risk who will be followed longitudinally, has been one of the first efforts that has brought sites together towards specific common objectives. Additionally, as an early demonstration of innovation from within the network, a DPUK-funded experimental medicine study, focused on the evaluation of a novel radioligand (Matthews, PI), has been initiated.

### Network working groups are addressing common issues of:

- Harmonising image acquisition and analysis with the creation of study "toolkits" and generation of standardised image processing pipelines
- Setting up guidelines for best practice for protocol design, process control, consents, subject safety and data sharing
- Making radioligands needed for dementia studies as widely available as possible across the UK by coordinating use of network radiochemistry resource
- Study set-up and governance.

### Specific objectives over the next year include:

- Evaluation and optimisation of advanced MRI-based PET attenuation correction methods developed by network leads (Ourselin et al., UCL; Hammers et al., King's College) to enable quantitative scanning without the need for CT radiation exposure
- Development of robust protocols based on reduced doses of radioligands, further minimising radiation exposure to subjects and better enabling longitudinal PET studies
- Further development of MRI-based motion correction algorithms to enhance effective resolution in scanning
- Initiation of major multi-site scanning protocols for new network-based studies, including the EC-funded AMYPAD and the MRC Deep and Frequent Phenotyping Study.

The MRC DPUK Imaging Network is now live! We believe that the infrastructure, cooperation across sites and commitment to joint working will make this resource internationally unique. There is no question that it has already begun to transform ambitions for UK dementia research.

*Newcastle's new GE Healthcare PET-MR scanner*
© Michael Firbank

## INFORMATICS NETWORK

**Network Lead**
**Professor Simon Lovestone, University of Oxford**

Iain Buchan
Andrew Bucknor
Richard Cain
James Cunningham
Mike Denis
Simon Ellwood-Thompson
Lars Engstrom
Roger Gunn
Christopher Hinds
Seth Love
Ronan Lyons
Clare Mackay
Elisa Majounie
Kate Mortimer
Chris Orton
Sebastien Ourselin
Karen Tingay
Julie Williams

***This network is aiming to enhance the ability of researchers to find and then use data and information collected in DPUK. This involves establishing a set of platforms that will improve researchers' ability to access the data within a safe and secure environment that respects data privacy and the Information Governance agreements, including consent and approvals of the cohorts collaborating with DPUK.***

### The objectives for the Informatics Network are:

1. Extending CRIS from three to 10 NHS regions (Oxford)
2. Creating a remote data collection platform using mobile devices (Manchester)
3. Designing and building a national image sharing and analysis platform (Oxford)
4. Establishing the infrastructure to underpin genetic analyses across DPUK
5. Providing digital archiving for brain banking (Bristol)
6. Increasing DPUK Data Portal processing speed and capacity (Swansea).

### UK-CRIS

CRIS is an innovative research solution that retrieves data from an NHS Trust's electronic medical record system, pseudonimises it to protect patient identities and then loads it into a database. This database can then be queried to perform a detailed range of research queries. UK-CRIS will build and expand on successful projects and will deploy the Clinical Record Interactive Search solution (CRIS) to an additional ten mental health trusts across the UK. UK-CRIS allows 'federated querying' (the ability to run research queries across data sourced from multiple trust organisations n=2M). In addition, UK-CRIS will seek to establish a linkage between CRIS data and UK Biobank.

### Remote data collection through wearables and devices

DPUK represents an ideal opportunity to develop and test the use of remote data collection through peripherals, wearables and other uses of pervasive or mobile computing technologies. In preparation for this anticipated substantial change in the way research and, ultimately, clinical data is collected, the team has established a platform for secure data management and analysis. In October 2015, three workshops were held, two with potential participants and one with clinicians, the purpose of which was to test devices relevant to dementia data collection. A report from these workshops is available on the website in the 'Research infrastructure' section. The team is now seeking researchers who would like to hire their resources and utilise the platform for analysis.

*DPUK wearables and devices: researcher workshop October 2015*

### Neuroimaging sharing and analysis platform

The objective is to create a national image-sharing and analysis platform for dementia research. The platform has a federated structure which is designed to manage, share and analyse multimodal imaging data associated with DPUK cohorts. The programme is establishing: 1) a catalogue of existing DPUK imaging data with a search and data request capability, 2) a Data Management System (DMS) designed and implemented at multiple sites using a generic data model, and 3) a central instance of the DMS with a capability to search for subjects across distributed sites, and to receive data from local sites for central data analysis. There is a DPUK imaging informatics node at each of the nine Imaging Network sites, with a central hub in Swansea and a specialist node at UK Biobank. Training and information dissemination are a priority for the next year. The infrastructure is already committed for studies, including the MRC DPUK PET-MR network, MRC UK 7T network, and MRC Deep & Frequent Phenotyping Study.

### Genetic data sharing and analysis platform

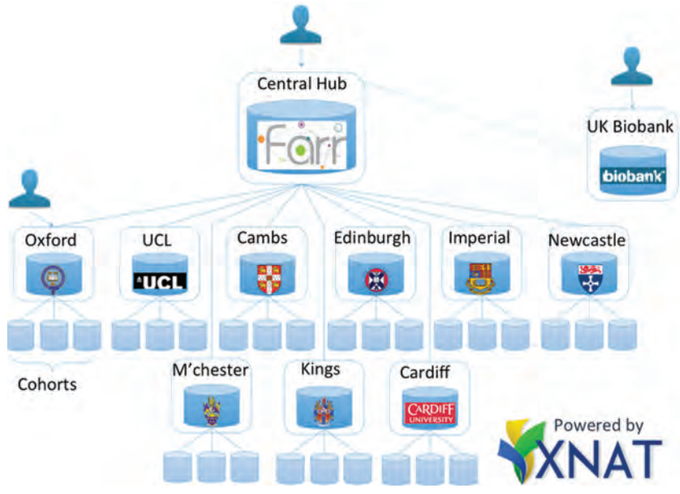
This component provides novel tools and software to share genomic data collected within the cohorts of DPUK and facilitate analysis of these rich datasets. The dedicated platform will:

- Facilitate and automate a variety of genomic analysis pipelines in a High Performance Computing (HPC) environment
- Develop a genotype data registry and cohort selector
- Provide a front-end genetic results data registry to capture new analyses results and facilitate meta-analyses.

Another key component is a results database: an online workspace for searching and identifying genes, Single Nucleotide Polymorphism (SNPs), and genomic locations of interest or with special relevance to dementia, which integrates summary data from different study cohorts for the purposes of aggregate data meta-analysis.

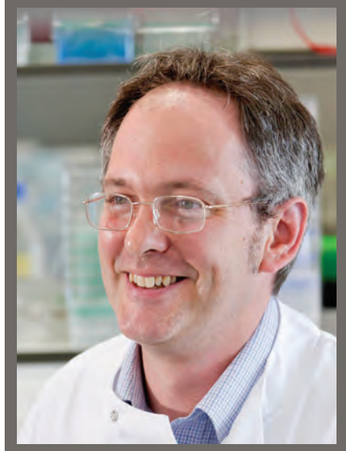
### Digital archiving for brain banking

Through DPUK a network of brain banks has been enhanced with facilities for digital archiving, including the use of barcode infrastructure to enable tracking of samples donated for research. The system will greatly reduce the work involved in the monitoring of brain bank activities by the MRC and other interested parties (eg the Human Tissue Authority and the charities that fund brain banks - MS Society, Parkinson's UK, ARUK, the Alzheimer's Society) and will facilitate extension to the DPUK brain donation programme.




*DPUK imaging network informatics showing the national distribution of nodes*

## STEM CELLS NETWORK



**Network Lead**
**Professor Richard Wade-Martins, University of Oxford**

Colin Akerman
Simon Lovestone

**Sally Cowley, StemBANCC and University of Oxford (Cellular reprogramming)**
Zameel Cader
John Davis
Julian Knight
Francesca Nicholls
David Owen

**Tom Warner, University College London (Cellular phenotyping)**
Adrian Isaacs
Parmjit Jat
Robin Ketteler
Rickie Patani
Sarah Tabrizi
Selina Wray

**Nicholas Allen, Cardiff University (Neuronal physiology)**
Yves Bardes
Lesley Jones
Paul Kemp
Emma Kidd
Emyr Lloyd-Evans
Anne Rosser
Julie Williams
Katie Lunnon, John Mill and Andy Randall (Exeter)

Vasanta Subramanian (Bath)
James Uney (Bristol)

**Siddharthan Chandran, University of Edinburgh (Glial biology)**
Ian Deary
Charles ffrench-Constant
Giles Hardingham
David Lyons
Tara Spire-Jones
David Wyllie

**Frederick Livesey, University of Cambridge (Genetics)**
Jenny Gallop
Steve Jackson

**Nigel Hooper, University of Manchester (Proteomics)**
Stuart Pickering-Brown
Tao Wang
Chris Ward

***Contributing to a systematic and coordinated programme of stem-cell research, the DPUK Dementia Stem Cell Network (DSCN) will support the development of iPSC-based enhancement of strategic DPUK cohorts.***

### Cellular reprogramming

**Establish automated culture of iPSC lines**

The Hamilton Stem Cell Automation Platform has been installed, commissioned and acceptance tests passed (Cowley, Oxford). To date, we have been through sequential stress tests/snagging phases, and have now trained seven users and implemented daily automatic media exchange of up to 70 plates across four different plate formats and eight media types in parallel. We are already operating at up to 50% capacity and expect to scale further over the course of the autumn.

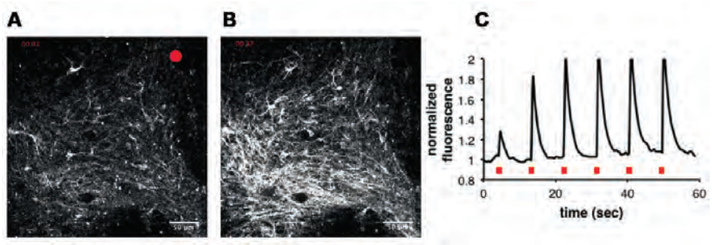



*Fig 1: Optogenetic control of human stem cell-derived cortical neural networks. 2-photon imaging of ESC-derived neurons expressing both the genetically encoded calcium sensor GCaMP6 and the red-shifted opsin variant C1V1. Stimulation at 590nm activates the opsin, driving neuronal activity, with GCaMP6 reporting network activity. Single images are shown of stimulation (A) and response (B). Time-resolved quantification of total neuronal activity in response to repeated stimulation is shown in (C).*

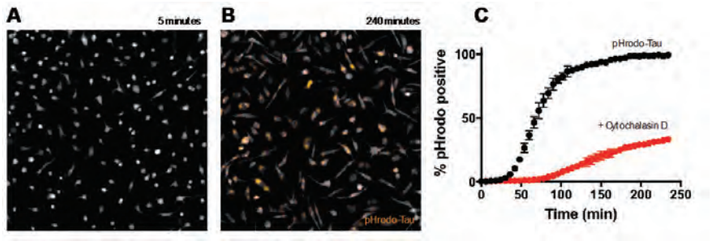



*Fig 2: Live imaging of endocytosis of tau protein by iPSC-derived microglia using the Opera Phenix. Tau was labelled with the pHrodo pH sensor that fluoresces at low pH, including when in acidic early endosomes. Still images 5 minutes (A) and 240 minutes after addition pHrodo-tau are shown. (C) Comparison of uptake rates in untreated (black) and Cytochalasin D-treated (red) cells. Inhibition of actin dynamics by Cytochalasin D significantly slows tau uptake by endocytosis.*



### Cellular phenotyping

**Establish protocols for neuronal differentiation across DPUK Stem Cells Platform**

We are in the process of introducing standardised protocols across the network. Cambridge provided a validated SOP for the generation of human cortical neurons (and astrocytes). This was developed in the Cambridge group, and was tested within the IMI StemBANC consortium as part of a study of the reproducibility of Alzheimer's disease phenotypes across six centres. Oxford has provided the validated protocol for the differentiation of dopamine neurons previously published as generating highly physiological dopamine neurons capable of revealing patient phenotypes.

**Establish common approaches for high-content imaging on Opera Phenix platform**

To establish common approaches for high-content/high-throughput imaging, Cambridge has developed methods for imaging of human neuronal and microglial endocytosis, both live and in fixed samples, using the Opera Phenix platform.

***Oxford has installed a second Opera Phenix platform which is up and running and in use for the imaging of dopamine neurons and astrocytes from PD patients. A third Opera Phenix machine has been installed at UCL. To develop common approaches for high content image phenotyping across the DPUK DSCN, UCL has studied a number of iPSC-derived cortical neuronal models of neurodegenerative disease and studied with both live cell and fixed samples.***

### Neuronal physiology

In Cardiff, use of the multielectrode array (MEA) and Seahorse analysis platforms is increasing and protocols to optimise research output are being developed. Notably, the technology is supporting collaboration across institutions. The MEA system has been used in an Oxford/Cardiff (Cowley/Allen) collaboration analysing IPSC-derived microglia and, importantly, use of DPUK equipment has extended beyond the immediate DSCN network to collaborations with Exeter (Randall) and Bristol (Uney).

### Functional genetics

**Functional analysis of fAD iPSC lines to model AD phenotypes**

As part of a wider ARUK-funded programme, Cambridge (Livesey) has developed and are optimising neuronal tau uptake assays (fig 2 opposite). Those assays will be the basis of the CRISPR-based functional screens in development for projects within the ARUK Stem Cell Research Centre, and for an OpenTargets project in collaboration with the Sanger Institute, EBI, Biogen and GSK.

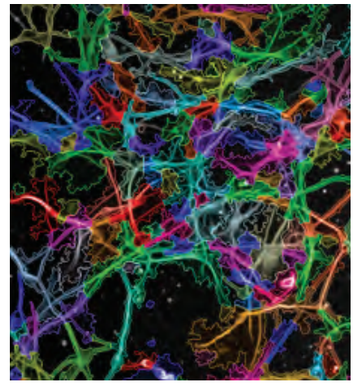


*Fig 3: iPSC neuronal network visualised using the find cytoplasm function of Opera Phenix to identify neurites and neuronal projections as discussed at UCL Imaging Network meeting*

**Functional analysis of PD iPSC lines to model PD phenotypes**

Oxford (Wade-Martins) has published PD GBA-N370S patient iPSC-derived dopamine neurons to have clear phenotypic deficits in ER stress, autophagic function and lysosome biology resulting in elevated alpha-synuclein release. This work has allowed us to develop robust assays suitable for high-throughput phenotypic screens using DPUK DSCN equipment: the ECHO Nanodrop, the Opera Phenix and the BMG Pherastar. Work will start with the SGC probe set and further libraries will be obtained from academic and industrial partners. Wade-Martins has obtained funding from the Oxford ARUK DDI for a post-doctoral scientist to undertake joint projects. There is also considerable interest in the work from industry partners and discussions for joint projects are ongoing.

### DPUK DSCN Network building

- All equipment purchased and installed
- MRC Partnership Grant awarded (PI: Chandran, Edinburgh)
- Monthly PI teleconferences throughout 2015/2016 (Wade-Martins)
- DPUK DSCN workshop to share and harmonise iPSc culture SOPs hosted in Dec 2015 at Oxford (Cowley)
- DPUK DSCN workshop to facilitate standardising neuronal differentiation methods and SOPs hosted in January 2016 at Cambridge (Livesey)
- PI face-to-face meeting in Manchester, June 2016 (Hooper)

# Experimental medicine

***The focus of the DPUK EM programme is to accelerate the development of interventions through identifying neuropathologic and neuroprotective pathways and mechanisms. The DPUK EM strategy is to facilitate synergy across disciplines and technologies, establishing expert working groups for specific research themes, each with an academic lead and industry partner support. Currently these groups are UK-based but international interest is welcome.***

***The DPUK EM working groups are encouraged to develop systematic and coordinated programmes of work that will be competitive for strategic funding. Given the complexity of these pathways and mechanisms, DPUK has prioritised three EM themes.***

## THEME 1: SYNAPTIC HEALTH

**Led by Professor James Rowe (Cambridge)** and **Dr Declan Jones (Janssen)**

Synaptic loss and regeneration is a highly dynamic process that persists throughout adulthood, and unlike neuronal loss which is irreversible, synaptic regeneration can be promoted. A greater understanding of synapse function, loss and repair would enable therapies to be developed to retard synapse degeneration and enhance synapse repair.

The strategy group has focused its attention on the development of a collaboration which establishes an innovative research platform for new therapies against Alzheimer's disease (AD), exploiting recent advances in disease mechanisms and emerging therapeutics. This includes academic groups with significant expertise in the use of MEG/EEG and tau PET imaging (Cambridge, Oxford, Cardiff), and Pharma partners with significant expertise in AD drug discovery, experimental medicine, and later clinical development, and with tau-associated assets (tau PET ligand, potential tau Ab for therapeutic clinical trial).

The aim is to transform the prospects for patients affected by AD dementia and those with mild symptoms from AD pathology (prodromal AD, also known as biomarker-positive mild cognitive impairment, MCI). Our results will also have major implications for strategies to treat other neurodegenerative diseases.

**Our specific objectives are to:**

1. Exploit advanced neurophysiology to characterise AD and MCI
2. Develop physiological markers of acute plasticity and disease progression, and test their response to a novel disease-modifying therapy
3. Promote mechanistically informed and efficient clinical trials, and disease modelling in silico.

The next immediate priority will be to extend the group to include the Stem Cell Network, Imaging Network, external companies and preclinical scientists for a series of workshops to build upon the current activities and expand activities to leverage the growth in the platform since the baseline.

## THEME 2: INNATE AND ADAPTIVE IMMUNITY

**Led by Professor Paul Morgan (Cardiff)**

Evidence implicating the immune system and inflammation in dementia is growing. A convergence of mechanisms has been observed in Alzheimer's disease (AD), Parkinson's disease (PD) and Amyotrophic lateral sclerosis (ALS), in which neuronal damage promotes neurotoxic microglial hyperactivity. Targeted anti-inflammatory therapies to regulate glial-related inflammatory response may have broad application across neurodegeneration. A working group is being formed to bring together genetics with inflammatory biomarkers in order to apply for strategic grant funding.



## THEME 3: VASCULAR DISEASE MECHANISMS (VDMs)

**Led by Professor Joanna Wardlaw (Edinburgh) and Dr Paul Wren (GSK)**

Photo of Professor Joanna Wardlaw
©Stefano Cagnoni (stefanocagnoni.com)

Epidemiological, genetic, neuroimaging and clinico-pathological data indicate vascular mechanisms as fundamental risk factors for dementia. These are intrinsic in vascular dementia with an extensive overlap between neurodegenerative and vascular factors defining significant mixed dementia populations. Considering that mixed dementia is the most common cause of dementia in the elderly, it has become increasingly important to harmonize basic science, translational and clinical approaches that include the integration of a deeper understanding of the contribution of peripheral and central vascular disease mechanisms in diverse dementia populations.

**The priority focus covers two areas:**

1. Experimental model and mechanisms workshop planning in parallel with a themed edition of Clinical Science
2. Evolving a vascular grant application focused on human participation.

A neuropathology workshop has resulted in improved communication and a grant application to ARUK. A special themed edition of Clinical Science will be published by the Biochemical Society focusing on vascular contributions to dementia and including contributions both from this group and from participants at the experimental models and mechanisms workshop which will be held next year.

## DPUK INVESTMENT IN EXPERIMENTAL MEDICINE

***The strategy groups have also worked to develop applications for DPUK to invest in small informative and pilot projects that will be used to inform the design of larger scale research projects that the group can then put forward for external grants.***

### 1. HOW DO PERIPHERAL AND CENTRAL VASCULAR MARKERS RELATE TO COGNITIVE DECLINE?

**Principal Investigator: Professor Ian Deary, University of Edinburgh**

This exploratory study will investigate statistical relations between measures of plasma lipidomics and lipoproteins and cognitive and neurovascular imaging parameters. The main hypothesis is that the lipidomic/lipoprotein markers will correlate with, and allow the stratification of, declines in the cognitive and neurovascular parameters.

With the rich and longitudinal cognitive and brain data in the cohort, it is possible to test hypotheses about lipidomics variables as both outcomes and potential causes of cognitive differences, and then map their associations with brain health, especially white matter.

Analysis of samples at the National Phenome Centre is underway to investigate the following:

- The individual lipidomic/lipoprotein/ Biocrates/SOMAscan profiles that may represent fit to cognitive performance
- The individual lipidomic/lipoprotein/ Biocrates/SOMAscan profiles that may directly associate with intermediary imaging markers of vascular disease burden including MRI variables: visible markers as individual (WMH, lacunes, PVS, global and regional atrophy) and combined SVD features (SVD burden score); and subvisible markers (MD, FA, T1, MTR in normal appearing white and deep grey matter)
- The individual lipidomic/lipoprotein/ Biocrates/SOMAscan profiles that may represent fit to cognitive performance in presence or absence of markers of cerebrovascular burden
- To specifically test the 10 lipid panel identified by Mapstone et al, 2014 as to whether it may represent fit to cognitive performance with evidence of cerebrovascular burden
- To specifically test whether PC16:0/20:4(5), PC16:0/22:6 & PC18:0/22:6 profiles may represent fit to cognitive performance with evidence of cerebrovascular burden to further enhance the King's Group established findings.

## 2. INTEGRATION OF CLINICAL AND CELLULAR PHENOTYPES IN THE MRC NIHR DEEP AND FREQUENT PHENOTYPE COHORT

**Principal Investigator: Professor Richard Wade-Martins, University of Oxford**

This project will test the hypothesis that the cellular phenotype-induced pluripotent stem cell (iPSC-derived) neurons from patients will recapitulate the clinical phenotyping using an extensively "deep-phenotyped" AD cohort. The use of iPSC-derived neurons allows us to study the cells affected in AD which have previously been inaccessible, hidden deep in the brain. We will compare for the first time the relationship between the level of Abeta pathology revealed by imaging a patient, with the response of cortical neurons and synapses derived from same patient to A-beta protein in a dish.

The value of this is that it allows use of the unique DPUK cohort and DSCN resources to investigate whether clinical phenotypes in sporadic Alzheimer's can be correlated with cellular phenotypes in neuronal cultures differentiated from patient-derived iPSCs. By combining the resources of the DPUK cohorts and the Stem Cell Network, this project will provide an exemplar for the integration of the study of dementia across DPUK.

**Progress to date includes:**

- The Oxford MRC DPUK Dementia Stem Cell Centre will generate iPSCs lines from the participants of the D&F Phen study. At least three lines per individual will be generated, quality control checked and banked using workflows previously established at Oxford. In parallel, we will receive 15 lines in an ApoE allelic series (5 ApoE2/E2, 5 E3/E3 and 5 E4/E4) reprogrammed by StemBANCC, adding great value to the proposed project. Lines will be differentiated into cortical neurons and brain endothelial cells using established DPUK DSCN and StemBANCC protocols. 21 individuals have been recruited through the DPUK D&P Phen study. 14 participants had amyloid [18F]AV45 tracer PET scanning and 12 of them also had tau [18F] AV1451 tracer PET imaging; 21 patient blood samples were obtained; five have been reprogrammed and are in expansion phase before QC testing; reprogramming has just been started for a further eight.
- We will compare the clinical response (using cognitive scales) to amyloid load in patient brain (determined by PiB scans), with cellular response (cell death, alterations in neuronal morphology and spine density) to applied amyloid load through Abeta peptide addition using high-content imaging. 21 participants had clinical tests of cognition (ADAS-Cog, MMSE, HVLT, CLOX) and computerised tests of cognition (CANTAB battery). An initial selection of five participants was based on their ratio of overall cortical amyloid to entorhinal cortex tau signal levels. A broad range of ratios was used to capture the variety of patterns of tau entorhinal cortex accumulation in response to cortical amyloid levels. In the full analysis, iPSC lines from the 12 participants with tau and amyloid imaging will be reprogrammed as well as one participant with amyloid imaging only.

## 3. MULTI-MODAL IMAGING CORRELATES OF ASTROGLIAL ACTIVATION, β-AMYLOID DEPOSITION AND NEURONAL ACTIVITY AS MARKERS OF COGNITIVE IMPAIRMENT IN AD

**Principal Investigator: Professor Paul Matthews, Imperial College London**

This pilot study will characterise the brain uptake of the novel astroglial activation imaging marker, [11C]BU99008, in AD subjects compared to non-AD control subjects. Relationships between [11C] BU99008 brain uptake, Abeta deposition and brain glucose metabolism will also explore how multi-modal imaging indices may inform. P**riorities are:**

- To test whether the uptake of a PET astroglial activation tracer ([11C] BU99008) is increased in the brains of people with mild to moderate AD relative to age-matched healthy volunteers
- To assess the correlation of PET-detected astroglial activation with regional reduction in FDG uptake
- To assess whether PET-detected astroglial activation co-localises with Abeta deposition.

A pilot multi-modal imaging study in 15 healthy versus 25 mild to moderate AD patients has been designed, and recruitment is underway with the first patient being scanned in February 2016.



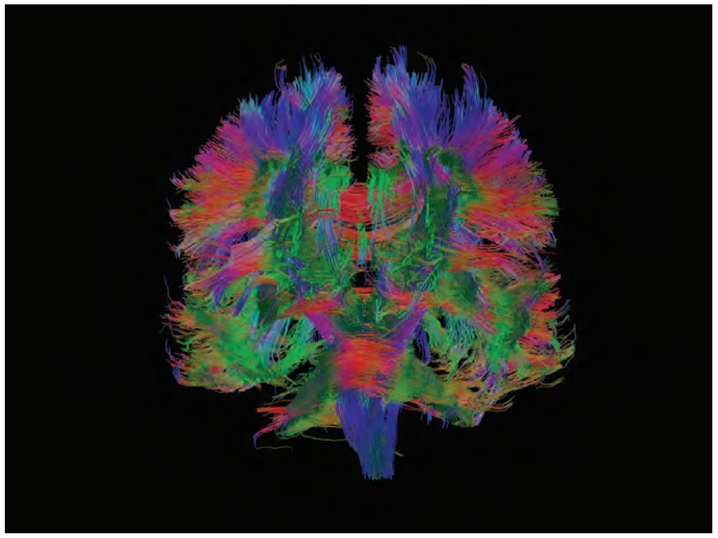
# Deep and Frequent Phenotyping

**Lead: Professor Simon Lovestone, University of Oxford**

### *Deep and Frequent Phenotyping to enable clinical trials for Alzheimer's prevention*

The challenge to generate disease-modifying therapies by 2025 is an enormously important one that can only be achieved by speeding clinical trials including early phase studies such as experimental medicine and proof of concept trials. A real obstacle to such studies is the lack of a tool or biomarker that could be used to measure change in disease in the preclinical or prodromal stage, the phase of disease where therapies are most likely to have a chance of efficacy. The Deep and Frequent Phenotyping Study is designed to identify such a marker by measuring a range of markers that might reflect disease activity and repeating these often over the period typical of a clinical trial, and then applying big data analytics to the enormous volumes of data collected.

Such a study places considerable demands on research participants. We therefore partnered with Alzheimer's Society to perform a feasibility and practicability study. The protocol entailed dual amyloid and tau PET imaging and then repeated measures of electrophysiology (EEG/MEG), imaging (structural and functional MRI), retinal pathology, gait, including using continuous measures from connected devices, conventional and tablet-based cognitive tasks and repeated sampling of blood and CSF. The Alzheimer's Society brought together a citizen advisory panel that helped in the generation of the study protocol and conducted quantitative and qualitative research on acceptability with participants. The feasibility study was implemented in sites from the NIHR Translational Research Collaboration in Dementia and during 2015 and 2016 we showed that implementation of the challenging protocol was not only possible but was acceptable to participants. Data analysis from this exploratory phase is underway and our plans now are to move to a full study in 250 participants during 2017 and 2018.



*Tractography of an LBC1936 participant. Illustrating level of brain structure detail to be observed in the Deep and Frequent Phenotyping Study. (© Dave Liewald_Mark Bastin)*

# Raising the DPUK profile

***A range of activities raised awareness about DPUK with its target audiences in 2015-2016.***

## Networks

The project established a cohort PI forum in 2015, with four engagement seminars: two in June, one in July and one in January. The first International Brain Banking Advisory Group meeting was held in January 2016. The objectives of this group are to advise and provide comment on DPUK's emerging strategies, to ensure careful, informed and affordable strategies for collection and curation, and to ensure the most informative science in the short, medium and longer terms from a brain donation programme within the platform. The first executive team meeting was held with international advisers in February 2016. The objectives of this group are to contribute in two major and equally important ways to the success of DPUK by explicitly providing an international perspective on its scientific programme and implicitly as international ambassadors for the work of DPUK.

## Events

The highlight of the year for DPUK was its inaugural Annual Conference, 'Tools for Science,' held on 26 April 2016. A programme of eminent researchers in the field of dementias, led by keynote speaker Professor Mike Weiner of the University of California, shared the latest findings. Topics included DPUK's role within the international research context, achievements in the high-technology networks, the DPUK cohorts and experimental medicine.

The work of many people within DPUK was celebrated. Three early career researchers presented their work, having been selected through a competitive process. Colleagues were able to share their work with conference attendees at the poster exhibition.

A post-conference pack which contains copies of presentations, abstracts and posters is available to view or download from the DPUK website. Videos of all presentations are also available to view. The Annual Conference 2017 will be held on 4 May in City Hall, Cardiff.


*Inaugural DPUK Annual Conference*
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# COMMUNICATIONS

## Newsletter

The e-newsletter launched in September 2015, providing an overview of the project's research and other activity. The second edition was published in January 2016. The newsletter goes to over 600 recipients.

## Annual report

DPUK's first annual report was produced in September 2015.

## Website

DPUK's full website – www.dementiasplatform.uk – was established a few months before the period of time that this report considers. During this period its aims were to reach out to both the public and scientific communities, to share key information about the project's aims and progress.

**Some key milestones include:**

- **August 2015:** the launch of the cohort directory and cohort matrix on the DPUK website
- **October 2015:** the launch of the data portal phase 1, providing access to the cohort finder and cohort profiles

## Social media

Currently, DPUK focuses its social media activity on Twitter, in order to share key project updates. Some key data on Twitter engagement can be found below for May 2016:

- 1,089 followers (115% increase on June 2015)
- 136,368 impressions (128% increase on June 2015)

## Media and publications

**Media:**

- 24 August 2015, BBC Radio Wales: Professor John Gallacher talks about dementia in Wales
- 5 November 2015, BBC Radio Manchester: Professor John Gallacher talks about DPUK's imaging network
- 25 February 2016, BBC Wales News (television): Professor John Gallacher talks about dementia
- 26 February 2016, radio interview: Professor Gallacher talks about a cohort study
- 14 April 2016, BBC Radio 4: Professor Paul Matthews discusses the imaging launch of UK Biobank and DPUK

**First research publication:**

- Professor Julie Williams et al, 'Common polygenic variation enhances risk prediction for Alzheimer's disease', Brain 2015: 138; 3673–3684

## Next steps

With a newly appointed communications team, there will be a comprehensive review of DPUK communications, with a new strategy to be agreed by the end of 2016.

# Wider connections

***The DPUK collaborative ethos extends beyond the current partnership and has developed in several ways during this second year.***

Within the UK, interest continues to grow in the support we can provide for other research programmes. This is welcome, and has led to two new academic partners: the University of Manchester and the MRC Biostatistics Unit at the University of Cambridge. Discussions are ongoing with potential industry partners. Academic and commercial organisations are invited to contact us to discuss what they might bring to the platform and how the platform can support their activity. DPUK has been and remains an active contributor to discussions on developing the UK dementia research-funding infrastructure with ARUK and the Alzheimer's Society.

It has also reached out to Parkinson's UK, the Stroke Association and the Motor Neurone Disease Association. Relationships have been built with the Drug Discovery Institutes, the Dementia Discovery Fund, the Translational Research Collaboration for Dementia (TRC-D), Join Dementia Research and the UK Brain Banking Network. These relationships lay foundations for future collaboration as opportunity arises. As DPUK establishes itself, nascent interest has been shown by other research communities in the wider utility of the DPUK infrastructure.

Internationally, DPUK continues to generate interest through presentations at AAIC (Toronto), the EMIF General Assembly (Budapest), IMI ROADS (Zurich and Barcelona), UKTI Expo2015 (Milan), MELODEM (Paris), and Hong Kong University, alongside international attendance at the DPUK annual conference. Interest in joining DPUK has been expressed by cohorts in North America, France and China (Hong Kong). The advantage to the cohorts is an immediate international profile, the advantage to DPUK is an enriched data corpus.

Relationships with other data-access infrastructures are developing on an opportunistic basis. Closer relationships are emerging with EMIF as DPUK adopts and adapts the meta-data interrogation tools developed by EMIF. Closer harmonisation of procedures is expected as DPUK and EMIF work together on the IMI ROADS project. Our ROADS proposal has been top-ranked for this award and final submissions to IMI are underway. Relations with GAAIN are constructive and will develop once the DPUK data portal is populated with cohort data.

We continue to support the open science agenda of OECD and proposals are before the Executive to appoint an open science champion to the steering group alongside an early career researcher champion.

Within Europe, DPUK is playing a central role in recruitment to the EPAD study led by Craig Ritchie (Edinburgh). EPAD is an innovative, adaptive phase two trial of anti-amyloid agents. During this past year this has involved recruiting staff, and identified suitable cohorts, in preparation opening four to five trial delivery centres around the UK. Comparable preliminary planning has also begun for the Deep and Frequent Phenotyping Study led by Simon Lovestone. Two DPUK researchers (Wardlaw and Rossor) have won CoEN awards, whilst DPUK is working closely with Joanna Wardlaw to add value to her JPND award on realising the value of cohort studies.

Transatlantic partnerships have been strengthened with presentations to and meetings with the Global Alzheimer's Platform and the Worldwide ADNI project, whilst a MoU has been signed between DPUK and the Canadian Longitudinal Study of Aging. We are exploring the possibility of a joint project with GAP and formalising a partnership between DPUK and ADNI. As the CCNA programme expands, we look forward to working more closely with CCNA and developing further links with Canadian researchers.

To provide an international perspective on our scientific programme, and implicitly act as international ambassadors for DPUK, Dr Maria Carillo (Alzheimer's Association), Professor Philip Scheltens (Vrije Universiteit Amsterdam), Professor Eric Reiman (Duke University) and Professor Lon Cardon (GSK: Pennsylvania) have generously agreed to be international advisers to DPUK.

*The global profile of DPUK grows, and our progress as we move from concept to function is observed with much interest.*



***DPUK is an active contributor to developing dementia research with many organisations***

# Director's overview of the second year

*Professor John Gallacher, Director*

*"Although procurement, grant, and conference success all indicate that DPUK is being effective in facilitating the development of a vibrant scientific community, this is only possible through the goodwill of a broad base of researchers."*

***To watch DPUK develop during the course of this second year has been gratifying. The enthusiasm and generosity shown by many individuals from across a large number of disciplines, from senior professors to early career researchers, has affirmed the value of a collaborative approach in pursuit of a common goal.***

## Strategic successes over the past year were:

1. Completion of the £33m CRI procurement to time and budget
2. Completion of the portal build
3. Engagement of new academic partners (University of Manchester, MRC Biostatistics Unit)
4. Awarding of three grants totalling £8m from the MRC Neuroscience Board to the Imaging and Stem cells networks, and for the Deep and Frequent Phenotyping Study
5. The DPUK 2016 scientific conference. This was fully booked, and the day was impressive for the quality and diversity of the presentations, the atmosphere of interest and enthusiasm, as well as the organisation.

All three network leads (Matthews (Imperial), Wade-Martins (Oxford), Lovestone (Oxford)) deserve credit for completing their CRI procurements to time and budget. Of particular note were the contributions of Paul Matthews (Imperial) and Andy Kordiak (Edinburgh), who carried the burden of establishing a transparent and scientifically-informed process for the Imaging Network. The result is highly satisfactory for DPUK, which now has the world's first cross-platform molecular and structural imaging network.

A major challenge this year has been completing the legal agreements enabling data transfer from participating cohorts to the DPUK portal, and data access by researchers to these data. This has delayed data transfer by several months. The deployment of additional resources has addressed this issue and it is anticipated that data transfer will begin Q3-Q4 2016.

The experimental medicine programme has received four expressions of interest this year, three of which were invited for full application, leading to one being funded to date, with the remainder in process. Overall 22 EoIs have been received and three projects funded. A more streamlined approach to this programme is required in order to accelerate the allocation of funding. This will be in place by Q3-Q4 2016.

The Executive Team and Steering Group have each met regularly and continue to shape the project. I would particularly like to thank Carol Brayne (Cambridge) for her support as Deputy Director over the last 12 months. Ian Deary (Edinburgh) will stand down from the Executive this summer and a process is underway to appoint a replacement from the University of Edinburgh. I would like to thank Ian personally for his highly supportive and constructive contribution to the platform throughout his membership of the Executive.

Although procurement, grant, and conference success all indicate that DPUK is being effective in facilitating the development of a vibrant scientific community, this is only possible through the goodwill of a broad base of researchers. But not only researchers: I would like to particularly acknowledge the support of the MRC at all levels in its constructive approach to the many challenges of delivering DPUK.



# Perspective from the MRC Oversight Board - Hugh Perry

*"The goal is to identify pathways and targets for diagnosis, monitoring and therapeutic intervention."*

***It is now more than 20 years since the origin of the amyloid hypothesis: a framework for investigating and understanding one of the most common dementias, Alzheimer's disease. Since then much has been learned about Alzheimer's, Parkinson's disease, frontotemporal dementia and the other dementias; the publications that fill our libraries bear witness to the creativity, insights and scholarship of many. It is also, however, apparent that these diseases of the brain are extraordinarily complex and the expertise required to address any one of them is not to be found in one laboratory alone, but will need "team science" on a scale that has not been previously in place.***

The Dementias Platform UK has demonstrated in the last two years that building a network to exploit the knowledge and diversity of the rich cohorts of the UK brings rewards. DPUK brings together scientists from no less than ten academic institutions and six company partners of very differing sizes. It has been in operation for only two years and yet it is already apparent that the creativity, diversity of skills and the collaborative spirit of these many individuals working together can and does make things happen. In the last year the three technology research networks – Imaging, Informatics and Stem Cells – have gathered momentum and, guided by their leads, have made remarkable progress, as outlined in this report. The experimental medicine themes have received seed funding that will enable them to develop proposals for larger-scale funding in the near future. There is much to do, but these two years have demonstrated that the base of this platform is secure and strong.

An important but challenging component of DPUK's activities is its outreach to the many different stakeholders involved in dementia-related research, including all the participants, the funders, and those who may benefit from the research in the short, medium and long term. Members of DPUK use diverse routes to communicate their message at scientific conferences, patient and carer-centred meetings and through social media. The findings of DPUK need to be elaborated and updated in different formats for different audiences, often with quite distinct expectations.

In the year ahead the MRC and its founder charity partners Alzheimer's Research UK and the Alzheimer's Society will establish the national Dementia Research Institute. This £250m investment will focus on discovery science of mechanisms that underpin our understanding of the dementias. The goal is to identify pathways and targets for diagnosis, monitoring and therapeutic intervention. The hub and centres model will create a network of world-class researchers with state-of-the-art technology at their disposal. It is therefore not hard to envisage that the complementary activities of DPUK and the Dementias Research Institute together will ensure that the UK is at the forefront of dementias research, with the very clear goal of making a difference to the lives of those living with dementia by finding routes to its early diagnosis, therapeutic intervention and prevention.

***Professor V Hugh Perry is Professor of Experimental Neuropathology within Biological Sciences at the University of Southampton. He is Chair of the MRC Neurosciences and Mental Health Board and Chair of the MRC Oversight Board for DPUK.***

# Industry perspective – Paul Wren, GSK

*"Strategic repurposing of selected cohorts for mechanisms discovery and trials readiness is also an important challenge that is being embraced by the platform."*

***To really understand the dementias and accelerate paths for transformative medicine development, it has always been appreciated that it will take time to build a platform which truly facilitates innovative collaborative research. However, as trust and active dialogue between partners of DPUK continues to evolve, it is clear that significant progress is being made on multiple fronts in line with the key deliverables of this project. The diversity of scientific, strategic and public engagement meetings sponsored by DPUK continues to grow the collaborative momentum.***

First and foremost, it is excellent to see that the bioinformatics, imaging and stem cell networks have completed their core infrastructure build. We have seen successful delivery of the data portal framework and supporting secure access processes, as well as procurement of state-of-the art equipment to enable harmonisation of methods and analyses and additional proposals for coordinated research programmes of work.

As the infrastructure has been built, experimental success is also taking shape. The completion and conversion of a Deep and Frequent Phenotyping pilot study to a full study has been supported by additional grant application success beyond initial DPUK funding. Equally, partnership grants have been awarded to the Imaging and Stem Cell networks to enable the infrastructure to be used to enhance their collaborative strengths.

DPUK has also provided seed funding to collaborative experimental medicine groups in diverse areas of science, ranging from vascular disease mechanisms, to innate and adaptive immunity and synaptic health. These groups, whether through such mechanisms, involvement with other consortia or being highly active in seeking large grant awards, have not only brought the communities together under the DPUK umbrella, but have also enabled processes within DPUK to become more efficient in facilitating collaborative science.

An integrated environment for dementias research relies not only on meeting the core deliverables through the sustained engagement of researchers at all levels and across all sectors, but also in providing opportunities for future innovative work. With the networks fully enabled and active, the portal ready to integrate cohort data, the EM groups bringing forward ideas and the work packages focusing on their key objectives and projected timelines, DPUK is well positioned as it enters its third year to continue to impact on the start-up, efficiencies and outputs of innovative, collaborative dementia research.

These first two years have therefore been very productive, involving iterative appreciations of best practice and laying down the core infrastructure and collaborative framework on which to build. Moving forward, populating the portal with cohort data through the continued navigation of ethical, legal and social issues in the management and utility of such fundamental datasets is a core delivery priority. Strategic repurposing of selected cohorts for mechanisms discovery and trials readiness is also an important challenge that is being embraced by the platform. These focused activities demonstrate the value and impact of DPUK and the significant role it will play in the coordination of the UK dementia research landscape and global strategies against dementia more broadly.

***Dr Paul Wren is a Senior Director in Neurosciences Clinical Development at GSK. He is a member of DPUK's Executive Team and Company Partner Forum.***



# Looking forward


*Professor John Gallacher speaking at the DPUK Annual Conference*

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***Building on last year's success, and the strength of our collaborations, I expect the year ahead to see an expansion in DPUK activity.***

***Our priorities for the year ahead are to populate the data portal, recruit from DPUK cohorts to clinical studies, and support further dementia-related funding applications. As cohort data are added to the portal we look forward to conducting the first cross-cohort analyses. For recruitment to clinical studies we are liaising closely with the IMI-funded EPAD trial and the MRC-funded Deep and Frequent Phenotyping Study. In relation to funding we will support DPUK researchers to submit a range of platform-based strategic grant applications.***

***Although these activities have value in their own right, it is important to remember that they break new ground for dementia research and will provide valuable experience for an ongoing programme of incremental improvements to the performance of the platform.***

***To see these programmes through, Professor Julie Williams of Cardiff University will be Deputy Director for this year and Professor Siddharthan Chandran of the University of Edinburgh will join the Executive Team. Julie's expertise in the link between genes and complex neurodegenerative disorders, as well as her role as Chief Scientific Adviser for Wales, will be very welcome in this position of leadership. Siddharthan's expertise in neurodegeneration and repair brings an added dimension to the platform.***

***In the coming year we will increase our commitment to early career researchers (ECRs) and open science. Over 20 ECRs are already funded through DPUK, and Professor Kim Graham has been appointed to develop ECRs' access to DPUK and its experts. Professor Clare Mackay has been appointed as our Open Science Champion and will be looking for opportunities to improve and expand access to DPUK data.***

***We look forward to our continued work this year as DPUK's progress is consolidated and we begin to share our research and outcomes at our conference in May 2017.***

***Professor John Gallacher, PhD AFBPsS CPsychol FFPH***
***Director, MRC Dementias Platform UK***

# APPENDICES

## Contents





# Conference abstracts from the three DPUK early career researcher prize-winners, 2016

### *Identifying dementia cases in large cohort studies using routine health data*

AUTHORS

**Dr Tim Wilkinson** (Clinical Research Fellow), **Dr Christian Schnie**r (Senior Epidemiologist), **Ms Amanda Ly** (Data Analyst), **Prof Cathie Sudlow** (Professor of Neurology & Clinical Epidemiology, UK Biobank Chief Scientist)

CONTACT DETAILS:

Tim Wilkinson: tim.wilkinson@ed.ac.uk; 07920037769; Centre for Clinical Brain Sciences, Chancellor's Building, University of Edinburgh, 49 Little France Crescent, Edinburgh, EH16 4SB

INTRODUCTION

Accurately identifying dementia outcomes in large population-based studies such as UK Biobank (UKB) is a DPUK priority. UKB follow-up is chiefly via linkage to routinely-collected, coded health data from hospital admissions, death registrations and primary care. In this pilot study, we investigated accuracy of these for identifying dementia cases in UKB.

METHODS

We identified Edinburgh-based UKB participants with an ICD-10 or primary care (Read V2) dementia code in at least one of these data sources, and extracted relevant correspondence from their NHS electronic medical records (EMR). A neurologist adjudicated each case, providing the reference standard for calculating the proportion of dementia cases correctly identified (positive predictive value [PPV]) by all data sources combined and each separately.

RESULTS

Among 17,000 Edinburgh-based participants (median age 57 years at recruitment in 2007/8), hospital and death data were available to 2012 with primary care data for 12,000 to 2013. 46 participants had a dementia code in at least one data source. 44 of these had available EMR data. PPVs for dementia were 41/44 (93%, 95% CI 81-99) overall, 13/15 (87%, 95% CI 60-98) for hospital admissions, 2/2 (100%, 95% CI 16-100) for death registrations, 33/34 (97%, 95% CI 85-100) for primary care, and 7/7 (100%, 95%CI 59-100) for participants with codes in ≥2 datasets.

CONCLUSION

Routinely-collected health data may be sufficiently accurate to identify dementia outcomes in UK population-based cohorts. We plan to extend this study to longer follow-up times and other regions to increase sample size, investigate dementia subtypes and assess generalisability.

## *Using an enhanced UK Biobank cognitive assessment to predict cognitive decline and dementia*

### AUTHOR
**Chloe Fawns-Ritchie**

### CONTACT DETAILS:
Ms Chloe Fawns-Ritchie: c.fawns-ritchie@ed.ac.uk,; 0131 650 8317; 7 George Square, Edinburgh, EH8 9JZ

### DESIGN
An enhanced UK Biobank (UKB) cognitive assessment has been developed to better estimate levels of prior cognitive ability and people's relative cognitive decline. This enhanced assessment, alongside the previous cognitive tests in UKB, will be used to investigate the relationship between levels of, and change in, cognitive ability in UKB participants, and to use this information to contribute to the prediction of who is at risk of developing dementia.

### METHODOLOGY
We engaged in a project to enhance the cognitive assessment in UKB by including brief tests of non-verbal reasoning which are sensitive to cognitive ageing, and additional tests assessing executive functioning and declarative memory: abilities known to decline in Alzheimer's disease and other dementias. A vocabulary task, an ability which stays relatively stable over the adult life course, has been included to help estimate prior cognitive ability.

### RESEARCH RESULTS
Using the current UKB cognitive tests, we are carrying out research investigating predictors of cognitive ability. Using polygenic risk scores, we found significant associations between polygenic profiles for several health conditions and cognitive test scores (Hagenaars et al., 2016). Those with a higher polygenic risk for Alzheimer's disease, for example, performed more poorly on the pairs matching and verbal-numerical tests.

### CONCLUSION
Using this enhanced, brief cognitive assessment, alongside the genetic brain imaging, health and lifestyle information in UKB, we can investigate the feasibility of predicting who is at risk of showing more severe cognitive decline, or developing dementia/neurodegenerative diseases.



## *DPUK sensing platform – Supporting future dementia research using wearable technologies with longitudinal data from everyday life*

### AUTHORS
**Matthew Machin, Lamiece Hassan, Daniel Cave, Rajesh Bhadra, John Ainsworth**

### CONTACT DETAILS:
Matthew Machin: matthew.machin@manchester.ac.uk; 0161 306 7381; Centre for Health Informatics, Room 2.007, Vaughan House, Oxford Road, University Of Manchester, M13 9PL.

### DESIGN
The DPUK Sensing Platform was developed to enable future dementia research using wearable devices and smartphones. A co-production approach was used to define the requirements. An agile development methodology was used to respond rapidly to changing requirements.

### METHODOLOGY
Five separate workshops were held with (i) researchers from public and private sector and (ii) patients from four distinct patient user groups. Patient feedback was sought on suitability and acceptability of wearable devices. Researchers provided their views on this as well as the overall functionality they wanted from the platform. Perspectives provided at the workshops were used to develop and refine the software.

### ORIGINAL DATA AND RESULTS
AFeedback from researchers and patients around wearable devices was consistent. Both groups wanted a platform that would support the widest possible range of devices. Researchers also wanted the platform to enable a wide range of future research projects. This led to the development of a platform that collects and stores data in a generic device-agnostic manner. The platform architecture was designed to be as flexible as possible to allow for future modifications.

### CONCLUSION
The Sensing Platform provides (i) a secure data warehouse, (ii) a web-based interface for researchers to configure their specific projects, (iii) the facility to have devices upload data on a regular basis or for a manual upload, (iv) the potential to integrate with other related platforms. This should allow the platform to support a wide range of future research projects in dementia.

# DPUK events

***DPUK has held and attended events to promote the activities of the platform and to encourage collaboration. A full list of events held is shown below.***

| DATE | EVENT | LOCATION | DPUK REPRESENTATION |
|---|---|---|---|
| 2 July 2015 | Cohort engagement seminar | Edinburgh | To provide an overview of DPUK, build relationships with cohorts |
| 16 July 2015 | Oxford Dementia Research Day | Oxford | Professor John Gallacher spoke at this event on the progress and development in the DPUK programme. |
| 18-23 July 2015 | Alzheimer's Association International Conference | Washington, DC | Professor John Gallacher presented alongside Sid E. O'Bryant (Interim Director – Institute for Aging & Alzheimer's Disease Research, University of North Texas Health Science Center) |
| 22 July 2015 | Longitudinal Studies: Maximising their Value for Ageing Research | Cambridge | Professor John Gallacher presented in Session 5 – Integrative Analysis of Longitudinal Studies on Ageing and Dementia |
| 26 August 2015 | Farr Institute International Conference 2015 | St Andrews | DPUK had two posters from WP2 at this conference for researchers, practitioners and policymakers interested in record linkage and the use of routine health data in their research |
| 15 September 2015 | ASCEND and REVEAL – investigator meeting | Saïd Business School, Oxford | Professor Gallacher presented on cognitive function and dementia at the annual UK investigators' meeting for the ASCEND and REVEAL trials in Oxford in September arranged by the Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU) |
| 20 September 2015 | Promoting data sharing in dementia research | Stockholm | This INCF-OECD workshop brought together policymakers, funders, and leading scientists to consider the barriers to data sharing in relation to dementias research and to begin to identify practical steps that can be taken to advance data sharing in this field. Clare Mackay represented DPUK at this event. |
| 28 September 2015 | Great Week: HEALTHCARE | Milan | Professor John Gallacher presented 'Responding to the Challenge – Collaboration Drives Acceleration of Research Outcomes' |
| 6 October 2015 | DPUK clinicians and researchers workshop | Manchester | The Wearables and Connected Devices component of the DPUK Informatics Network: workshop focused on the new research platform |
| 13 November 2015 | Brain banking workshop | London | To connect the vascular disease mechanisms group with the Brain Banking Network and DPUK |
| 9 December 2015 | Precision Medicine Conference | London | Professor John Gallacher presented 'MRC DPUK (Dementias)' |
| 2016 | | | |
| 14 January 2016 | School of Medicine 'Science in Health' public lecture | Cardiff | Professor John Gallagher spoke at a public medical lecture which aimed to open up areas of concern in health care and to inform the public about current medical research |
| 15 January 2016 | DPUK cohort engagement seminar | London | To provide an overview of DPUK, build relationships with cohorts and formally invite cohorts to be part of DPUK |
| 25 January 2016 | Vascular disease mechanisms workshop | Oxford | Bringing together experts in vascular disease and experimental medicine: vascular interaction with DDI and experimental medicine |
| 17 March 2016 | IMI EMIF | Budapest | Professor John Gallacher presented at the meeting |
| 14 April 2016 | ARUK scientific meeting | Cambridge | Professor John Gallacher presented at the meeting |
| 6 May 2016 | Generation Scotland Symposium | Edinburgh | Chris Orton and Karen Tingay attended to enhance engagement between DPUK and cohorts based in Edinburgh |
| 17-19 May 2016 | EPAD Consortium meeting | Barcelona | Professor John Gallacher presented at the meeting |
| 17 and 18 June 2016 | International Alzheimers Disease Conference | International Alzheimers Disease Conference | Professor John Gallacher presenting at the meeting |

# DPUK work package timeline

**KEY**

- Infrastructure
- Dementias Resource
- Experimental Medicine Strategy
- Methods Development
- Experimental Medicine Projects

| | Work Package | Principal Investigator | July 14 | Jan 15 | Jul 15 | Jan 16 | Jul 16 | Jan 17 | Jul 17 | Jan 18 | Jul 18 | Jan 19 | Jul 19 | Dependent Deliverables |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **1** | Cohort Profiling | Craig Ritchie | | Cohort Profiling and Tools | | | | | | | | | | Complete |
| **2** | Data Portal | Ronan Lyons | Data Portal - Design, Build, Management | | | | | | | | | | | |
| **3** | Trials Readiness | John Gallacher | Trials Readiness - Imaging 10,000 / Brain Donation | | | | | | | | | | | |
| **4** | Amyloid Cohort | Nick Fox / John Schott | Imaging and CSF screening - Tau and Amyloid | | | | | | | | | | | |
| **5** | FAD Cohort | Martin Rossor | | | Biomarkers - FAD / FTD / HD / AD | | | | | | | | | |
| **6** | Biomarkers | Simon Lovestone | | | | | Biomarker Discovery | | | | | | | |
| **7** | Synaptic Health | James Rowe | | EM Theme 1 - Synaptic Health Strategy Group | | | | | | | | | | |
| **8** | Immunity | Paul Morgan | | | | EM Theme 2 - Immunity | | | | | | | | |
| **9** | Outcomes Adjudication | Cathie Sudlow | Outcomes Adjudication - UK Biobank | | | | | | | | | | | |
| **10** | Cognitive Assessment | Ian Deary / John Starr | Cognitive Assessment - UK Biobank | | | | | | | | | | | |
| **11** | Trials Recruitment | Craig Ritchie | | | Closed | | | | | | | | | Resources re-distributed |
| **12** | ELSI | Carol Brayne / Shirlene Badger | | ELSI | | | | | | | | | | |
| **13** | Brain Donation | Carol Brayne / Paul Francis | | Brain Donation | | | | | | | | | | Oustanding Actions transferred to WP3 |
| **14A** | Biostatistics - Genetics | Julie Williams | | Genetics - Poylgenic Risk Score | | | | | | | | | | |
| **14B** | Biostatistics - Methods | Sylvia Richardson | | | | Biostatisical Methods | | | | | | | | Data Portal - Cross Cohort Analysis |
| **15** | Vascular Disease Mechanisms | Joanna Wardlaw | | EM Theme 3 - Vascular Disease Mechanisms Strategy Group | | | | | | | | | | |
| **EM1** | How do peripheral and central vascular markers relate to cognitive decline? | Ian Deary | | | Vascular markers and Cognitive decline | | | | | | | | | |
| **EM2** | Integration of clinical and cellular phenotypes in the DPUK Deep and Frequent Phenotype Cohort | Richard Wade-Martins | | | | Clinical and Cellular Phenotypes in DfP Cohort | | | | | | | | |
| **EM3** | Multi-modal imaging correlates of Astroglial activation, β-amyloid deposition and neuronal activity as markers of cognitive impairment in AD | Paul Matthews | | | | Multi modal imaging - cognitive impairment in AD | | | | | | | | |
| **EM4** | Crosstalk: The Impact of Cardiac Anatomy and Function on Brain Structure and Health | Steve Williams | | | | | Cardiac Anatomy and Function on Brain Structure | | | | | | | |

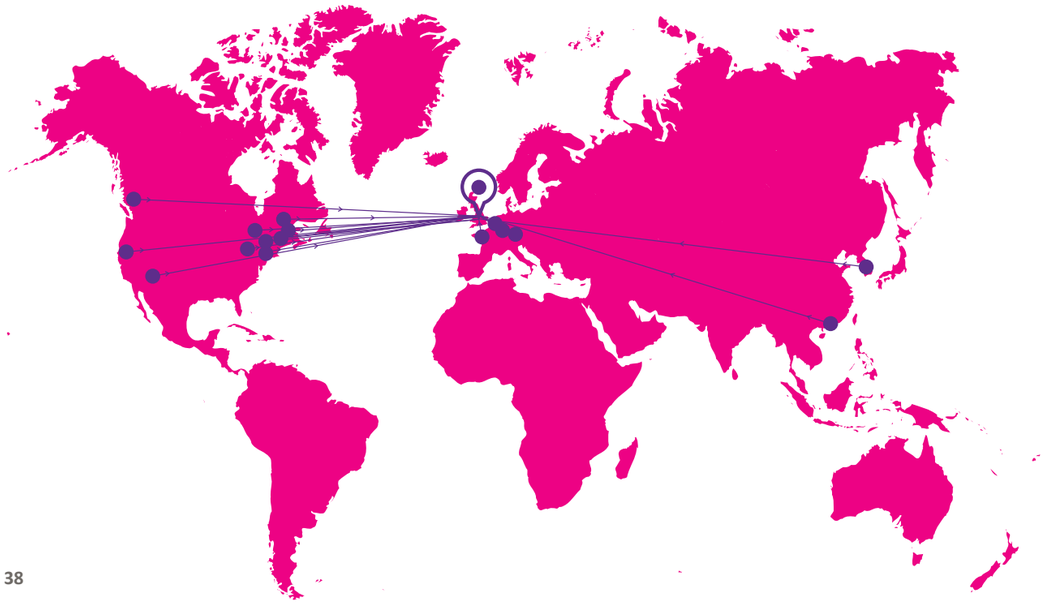
**Current period**

# **DPUK's reach:** people in contact with the project

## Number of DPUK contacts at UK universities:

- Aberdeen: 8
- Bangor: 1
- Birmingham: 2
- Bournemouth: 1
- Bristol: 8
- Cambridge: 30
- Cardiff: 13
- Dundee: 2
- Edinburgh: 39
- Exeter: 10
- Glasgow: 1
- Imperial: 31
- KCL: 15
- Leicester: 1
- LSHTM: 1
- Manchester: 17
- MRC BSU: 4
- National Phenome Centre: 2
- Newcastle: 18
- Nottingham: 1
- Oxford: 29
- Queen Mary London: 1
- Sheffield: 5
- Southampton: 3
- St George's: 2
- Sussex: 1
- Swansea: 5
- UCL: 45
- West London: 1
- Warwick: 1
- York: 2

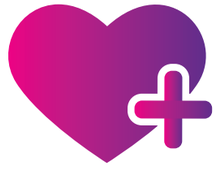
## International academic institutions with which DPUK has contact:



## Number of DPUK contacts at commercial organisations:

- Araclon Biotech: 4
- Autifony Therapeutics Ltd: 1
- Cambridge Cognition: 3
- Cerespir Incorporated: 1
- Clinchem: 1
- Covance: 1
- Digital Health Labs Ltd: 1
- Dunnech Global Ltd: 1
- Eclipse Experience: 1
- Eisai: 1
- Eli Lilly: 2
- Exprodo Software: 1
- Find Signage Ltd: 2
- GE Healthcare Life Sciences: 3
- General Pharmaceutical Council: 1
- GlaxoSmith-Kline: 13
- Holmusk: 1
- Imanova: 10
- Innovate UK: 1
- Inventiv Health: 1
- Ixico: 9
- Janssen: 26
- Life Plus: 1
- Lilly: 2
- London North West Healthcare: 1
- MedImmune/ Astrazeneca: 12
- Mentis Cura: 2
- Meso-Scale: 1
- Nesta: 2
- Notakey: 1
- Novartis: 2
- Olink: 1
- P1vital: 1
- PA Consulting: 1
- Pfizer: 1
- Phenome-nome: 1
- PPD: 1
- Proteomics: 1
- Re:Cognition Health Ltd: 1
- Reena Pharmacy: 1
- RiverRock: 1
- Roche: 6
- Sage Bionetworks: 1
- Science Practice: 1
- Siberia: 1
- Siemens: 3
- Somalogic: 5
- SP+EE: 1
- SVLSA: 1
- Takeda Cambridge: 1
- The Info Group: 1

## Charities and funders:



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Dementias Platform UK

Medical Research Council