



Dementias
Platform^{UK}
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OUR PARTNERS:



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VISION TO VALUES



Our vision and mission

Families, friends, employers and economies become free from the pain and cost of dementia thanks to the living legacy of population studies.

Our mission is to use the power of cohorts to accelerate the development of new treatments for dementia.



Our challenge

Dementia is a global health issue, affecting 46.8 million people worldwide. Research is critical to finding treatments, cures and prevention for dementia.



Our response

Dementias Platform UK contributes to dementia research through its:

- 1 Data Portal: the most accessible, large scale repository of population study data available to researchers anywhere in the world
- 2 Clinical Studies Register: enabling effective clinical trials through population study participants
- 3 Experimental medicine activity: conducting innovative studies into the mechanisms underlying dementia.



Our values

We are an intellectually generous community sharing data, best practice and technologies.

We are a creative community harnessing new ideas, new technologies and new ways of working.

We are a collaborative community inviting all stakeholders to join our programmes and shape our activity.

We are an enabling community, facilitating the leverage of further resources for dementia research.

WHERE WE WERE FIVE YEARS AGO



Long before the first hallmarks of dementia appear, significant changes are taking place in the brain. This presents a huge challenge for the scientific community: how do we find treatments at the early stages when we have the best chance of success? In over 100 years since the signs of Alzheimer's disease were first seen under a microscope, no one has found the answer.



The vision of DPUK was to bring this cottage industry of separate cohorts together, to support it, and to maintain it at the highest standards possible so it becomes the richest dataset for dementia research and treatment development.

Like many of my colleagues I recognised that the future of medicine is in big data. However, we don't just need big data for the best research insights – we need quality data. When we consider dementia, quality data means continuous and long-

term health records, it means detailed brain scans, it means genetic information – and it means easy access to all of this. Over 50 long-term health studies, known as cohorts, have been assiduously collecting this type of information year-on-year for decades. Science needs this quality data, but small numbers are of limited use. We need these data at scale. Researchers need to be able to use it at scale.

The vision of DPUK was to work with all the cohort studies – big and small, specialist and non-specialist – and the pharmaceutical industry to create the resources and technical infrastructure needed to conduct better science and reinvigorate the drug development pipeline for dementia.

The challenges implicit in this were manifold. Many were technical: data storage, data security, standardisation. The implications of using existing cohorts for treatment research and trials presented ethical and methodological challenges that had never been considered before. Industry was not well connected with university research.

Our vision was to bring this cottage industry of separate cohorts together, to support it, and to maintain it at the highest standards possible so it becomes the richest dataset for dementia research and treatment development. Our vision

was to optimise a rich heritage of health data collection, powering it with state-of-the-art technology to face one of the biggest global health challenges of our time: finding ways to prevent and treat dementia.



Professor John Gallacher
PhD AFBPsS CPsychol FFPH
Director of Dementias Platform UK

*Photo: John Gallacher, DPUK Director
Credit: Anna Lukala*

OUR ACHIEVEMENTS IN FIVE YEARS

We set out to transform the way dementia research is done through harnessing the unique power in the data collected by long-term studies of health, known as ‘cohorts’. Thanks to the extraordinary richness of cohort data we have been able to optimise the environment for conducting experimental medicine (EM) for dementia.

We have done this through large-scale investments in state-of-the-art technology, innovative collaborations with the pharmaceutical industry, and a new vision for the challenge that dementia presents.

OUR ORIGINAL OBJECTIVES	HOW WE’VE MET THEM	HOW WE’VE GONE BEYOND IN THIS AREA
<p>Data integration</p> <p>1. Integration of multiple cohorts into a dementia epidemiologic research platform, enabling rapid assimilation of evidence, identification of evidence gaps and testing of hypotheses.</p> <p> <i>This objective focused on bringing individual health studies together to create a larger, richer dataset for research and drug discovery in dementia.</i></p>	<ul style="list-style-type: none"> • DPUK collaborates with 47 different cohorts. • The Data Portal holds metadata for over 2 million individuals from these 47 cohorts. At the time of writing, researchers can work with data from 33 cohorts. • 63 formal applications for data have been received, from a community of 99 researchers across seven countries worldwide. 32 research studies have received data access approval. 	<ul style="list-style-type: none"> • We are pursuing data linkage opportunities with NHS Digital, NHS Wales and the Office for National Statistics. • The Data Portal is attracting international interest with a partner project beginning in Korea and discussion under way in Canada and the US.
<p>Data access and data analysis</p> <p>2. Development of a single bioinformatics portal accessing and analysing data across cohorts.</p> <p> <i>This objective focused on creating an online space where scientists can work with data from more than one cohort.</i></p>	<ul style="list-style-type: none"> • The Data Portal collates 22 broad categories of data. • DPUK’s imaging informatics platform offers 200 TB of central space to store and share brain scan data. • A suite of genetics exploration tools and free analytics software makes cohorts’ genetic information more accessible. 	<ul style="list-style-type: none"> • We have held a datathon jointly organised with the Alan Turing Institute and Deep and Frequent Phenotyping study, extending analytics of multimodal dementia data beyond the normal user range.



DPUK collaborates with 47 cohorts.

OUR ORIGINAL OBJECTIVES	HOW WE'VE MET THEM	HOW WE'VE GONE BEYOND IN THIS AREA
<p>Data enhancements</p> <p>3. Creating dedicated research resources by repurposing selected cohorts for dementia mechanisms discovery and trials readiness by:</p> <p>a) enhancing the UK Biobank imaging cohort with re-imaging at 2 years and trials readiness</p> <p>b) enhancing the 1946 birth cohort with amyloid imaging</p> <p>c) enhancing familial risk cohorts with Tau imaging</p> <p>d) creating a genetics risk cohort for proteomic studies.</p> <p> <i>This objective focused on enhancing particularly important health studies with additional data collection so they are optimised for discovery of key biological mechanisms in the development of dementia.</i></p>	<ul style="list-style-type: none"> • DPUK has agreed funding for 10,000 repeat scans in the UK Biobank cohort. • PET-MR imaging of around 500 participants in the long-running NSHD birth cohort is complete, creating a highly detailed image resource for the study of amyloid. • We increased the availability of familial disease data through supporting recruitment to the GENFI study. • We are creating a genetic risk cohort by recruitment through the Generation Scotland cohorts. 	<ul style="list-style-type: none"> • We have created a cohort-focused common data model.
<p>Data methods</p> <p>4. Fill methodological gaps preventing the conduct of population and EM studies by:</p> <p>(a) identifying and characterising dementia-related outcomes more accurately</p> <p>(b) developing new ways of assessing cognitive decline in the population</p> <p>(c) discovering how best to recruit for EM studies</p> <p>(d) discovering how best to recruit brain and iPSC donors.</p> <p> <i>This objective focused on improving the methods that scientists use when conducting research: electronic health records, cognitive testing, stem cells and participant recruitment.</i></p>	<ul style="list-style-type: none"> • DPUK teams have looked at electronic medical records and genetic data, and have developed more accurate predictors of dementia risk in the population. • DPUK has developed a new model of recruitment to trials that decouples risk disclosure from the practice. 	<ul style="list-style-type: none"> • A DPUK team has developed enhanced cognitive testing procedures which have been rolled out in the UK's largest cohort, UK Biobank. Validation of the enhanced methods is now ongoing.
<p>Integrating university and industry</p> <p>5. Develop an integrated programme of experimental medicine in partnership with industry.</p> <p> <i>This objective was about joining up the research environment in the UK, supporting closer collaborations.</i></p>	<ul style="list-style-type: none"> • We have funded eight experimental medicine studies, of which two are multicentre studies, in partnership with industry. 	<ul style="list-style-type: none"> • We have supported the development of communities of expertise. Researchers from different universities and industry come together to develop new study proposals. • The Stem Cells Network equips university researchers with industry-level technology, facilitating close partnerships and resource sharing with industry. • DPUK funded PET-MR scanners in five UK sites, now part of a seven-site UK-wide Imaging Network, enabling large multicentre studies such as DFP and EPAD.



DATA PORTAL

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There are so many opportunities in the Data Portal. I look forward to seeing where my analytical skills will take me now I can access the data in large population cohort studies.

DR SARAH BAUERMEISTER, SENIOR RESEARCHER

DATA PORTAL: IMPROVING ACCESS TO HIGH-QUALITY DATA

For the researchers who want to use their skills in the fight to find effective treatment for dementia, access to data has been one of the biggest barriers to testing new ideas.

Valuable relevant data are split up, hidden in individual researchers' records in their host institutions, and often available only to those who have the resources to collect it. We need the power of as many researchers as possible to know about and work with cohort data, not just a few. Dementias Platform UK has taken on the problem by turning the traditional model of data access on its head. DPUK brings researchers to the data, streamlining and fast-tracking data access. The result is fast-tracked science based on data of unprecedented quality for dementia.

Dr Sarah Bauermeister is one of the researchers who is using the Data Portal in her research.



NAME: Dr Sarah Bauermeister
POSITION: Senior Researcher
RESEARCH INTERESTS: early life and how this impacts on dementia risk
Credit: Anna Lukala

A NEW ERA OF DATA ACCESS

Save time: researchers make one application for data, whether from one cohort or several.

Cohort governance: access decisions will always rest with individual cohorts.

Administrative support: DPUK manages queries and fast-tracks responses to data applications.

Why did you embark on a career in dementia research?

I've always been interested in health, and finding out what people can do to stay healthy for as long as possible. Having worked with dementia patients and seen at first-hand the devastation of this disease both to the individual and their families, my motivation to pursue my research into cognitive decline is stronger than ever.

What are cohorts and why do you work with them?

Cohorts are research studies of the health of the same group of people, often conducted over decades. Regularly, the participants in cohort studies will have blood tests and complete questionnaires about their health and lifestyle. DPUK collaborates with 47 of these studies – taken together that's over 2 million participants, and it's difficult to overstate the importance of all these people for dementia research. We know dementia develops 15-20 years before any symptoms develop. As a series of snapshots of an individual's past, cohort data provides scientists with an amazing opportunity to learn more about the early phases of the diseases – so we can find the clues to prevention and treatment.

What can big data tell us about dementia?

When we talk about big data we're talking about datasets with tens of thousands of different variables, going into detail such as 'cigarettes smoked per day' or

'sandwiches eaten per week' for example. It means having this information at scale – not just for a few study participants but for thousands, and over long time periods. When I as a researcher have this breadth and depth of information, the analyses that I do are more robust and reliable. Working in this way is critical to achieving reliable insights into causes and treatment for dementia.



Data from long-term health studies, or 'cohorts', contain the clues to the processes and mechanisms involved in the development of dementia at its early stages – and potentially the clues to how we prevent or reverse these.

What are you investigating at the moment?

I'm investigating the impact of early life on later dementia risk. Do childhood adversity and poor mental health affect your risk of dementia? It is possible, and I'm using eight different datasets together in the DPUK Data Portal to test my ideas.

What are the challenges in your research?

A decrypted genetic dataset for half a million people – the UK Biobank dataset for example – is 14 TB in size. A single image scan could be around 1 GB. Researchers like me need to work with hundreds of thousands of these records. Many researchers simply don't have the PC processing power to cope with datasets of this size. The amazing thing about the Data Portal for me is that researchers don't need a supercomputer to work with this immensely rich data. They work on a virtual desktop, with access to software packages.

Are there any other problems you've faced as a researcher in this field?

Like many dementia scientists, I am interested in the characteristics and changes that take place long before we see the symptoms of dementia. I rely on data that's been collected over long periods of time. The data I want to work with may be owned by different data custodians, stored in different universities. It's not always obvious to me which records are available, who I need to get permission from, and how to arrange the physical transfer of data. The process is long and it's laborious. I don't want to be spending my time in this way – I want to be getting on with analysis and discovery.



Thanks to a long history of cohort data collection, the UK is the envy of the world. We are incredibly fortunate to have an immensely rich research resource today. The problem is, it's split up.

What is the potential of the Data Portal?

DPUK is making it possible – for me and all researchers, irrespective of our funding background, institutional alliance or career status – to work with high-quality dementia-relevant data. Scientists like me, working anywhere in the world, are able to find the data they need, and can analyse it easily too. Because of DPUK, dementia research has just become more hopeful, promising and optimistic, and all researchers should be incredibly excited about the opportunities available on the DPUK platform.

Since the Data Portal's launch in November 2017, 63 applications for data have been received.

The Data Portal is the hub of the Informatics Network which brings together cohorts' genetics, imaging, device and electronic health record data.

 **BETTER SCIENCE**

DPUK seeks to enable Sarah and thousands of other researchers around the world to get access to the data that could transform our understanding and treatment of dementia. The Data Portal offers the global research community:

- access to 47 cohorts
- free use of costly software packages (SPSS, SAS, STATA)
- streamlined administration.

In these ways, DPUK has simplified and opened up access to quality research data for dementia.

 **BETTER SCIENCE**
What is the value of detailed data?

It's not only the biggest datasets that are of most value to dementia researchers – science benefits from small, highly specialised data too. The DPUK team at UCL have been working with small cohorts of people with the rare familial forms of dementia. Detailed studies of disease progression in these cohorts allow scientists new insights that can then be tested in the larger cohorts.

Working with these small familial disease cohorts, the UCL team, led by Professor Martin Rossor, found that neurofilament concentrations in cerebrospinal fluid (CSF) can function as a useful sign of neurodegeneration. This is now being considered for inclusion in clinical trials of treatment.

DATA PORTAL IN PRACTICE



Since November 2017, **32 studies** have received data access approval.

DPUK is collaborating with **47 cohorts.**





Over **200 researchers** have attended DPUK training events.

99 researchers have applied for data access through the Data Portal.





Our average data application response time is **32 days.**

We've seen over **1,500** new visitors to the Data Portal website since its launch.





We've derived **22 data categories**, optimising existing datasets for studies into dementia.

Over **4,700** people have discovered DPUK resources and opportunities by visiting our website.



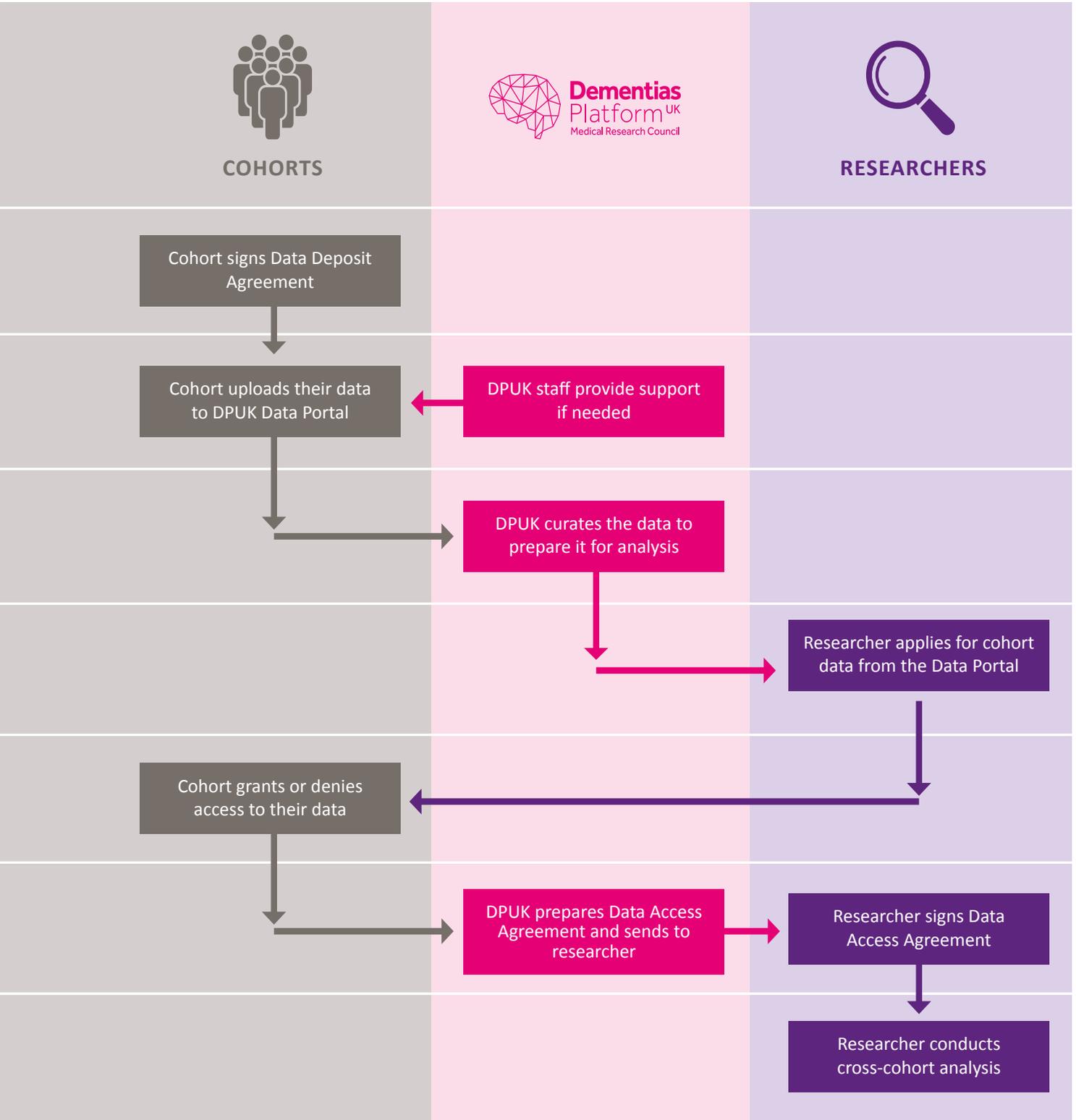


We've enabled researchers from **seven different countries** to access rich people data for their work, which enables better studies.

1	DATA DEPOSIT AGREEMENT
2	DATA UPLOAD
3	CURATION
4	APPLICATION
5	APPROVAL
6	DATA ACCESS AGREEMENT
7	ANALYSIS

HOW IT WORKS

We enable individual cohorts to benefit from world-class information security, whilst simplifying data access for researchers.



DATA ACCESS

DPUK has turned the traditional method of data access on its head through a novel vision: centralised storage and streamlined administration, but keeping access decisions with the original data custodians.

TRADITIONAL METHODS OF DATA ACCESS AND ANALYSIS	IN THE DATA PORTAL
 <p>Researchers mainly work with the data in their institution, on their own hard drives or rely on their Principal Investigator's contacts to get access to data.</p>	 <p>Researchers work with data collected by other institutions.</p>
 <p>Researchers make bespoke arrangements with individual cohort data owners for data access.</p>	 <p>Researchers use DPUK's data discovery tools to make one application for multiple cohorts.</p>
 <p>Researchers are unclear what data has been collected outside their institution and whether this data is available to them.</p>	 <p>Researchers see at a glance the data available in 47 cohorts. This is available to any researcher with internet access.</p>
 <p>Researchers don't know how long it will take to get access to the data they request.</p>	 <p>Our average data application response time is 32 days.</p>



More and more cohorts have genetic data now. This is very exciting – but genetic datasets are huge. I need the computing power to be able to process this data to allow me to test my ideas and to analyse it. The virtual desktop offers that.

DR SARAH BAUERMEISTER,
SENIOR RESEARCHER



The Data Portal is a world-class technical infrastructure that completely transforms the scale and detail of data that any researcher investigating dementia is able to work with. Far beyond just enabling access, the Data Portal is an online environment where researchers can actually conduct multimodal cross-cohort analyses.

CHRIS ORTON, DATA PROJECT MANAGER FOR DPUK



Thanks to the Data Portal, many researchers like me – without our own data – can try out our ideas on records from over two million people. This way, we can get closer to breakthroughs.

DR CHI-HUN KIM, EARLY CAREER RESEARCHER



CLEANING UP THE CHAOS: STANDARDISED DATA FOR FASTER ANALYSES

The data that researchers use in their work to understand dementia and how to treat it are not uniform or orderly: they are diverse, messy and complicated. Coding datasets in the same way makes the data usable.

It is a process known as creating a common data model, and it is a fundamental part of DPUK’s work in improving the quantity – and quality – of research data available for scientists.

Dr Chi Hun-Kim knows its importance.



NAME: Dr Chi-Hun Kim
POSITION: Early Career Researcher
RESEARCH INTERESTS: which factors cause dementia, how much impact they have on its development, and whether we can modify those factors to prevent dementia

Credit: Anna Lukala

Why did you embark on a career in dementia research?

I trained as a neurologist – a specialist doctor for brain conditions – and often I was in the position of having to diagnose my patients with dementia. Dementia has no treatment and I hated not being able to offer my patients hope. I decided to move into a research career so I could help find better options for preventing and treating dementia in the future. I’m trying to do my best for dementia patients through my research analyses.

You use multiple data sources in your research – why is that?

At the moment I’m conducting a study looking at the vascular factors –

characteristics of a person’s blood vessels, for example – involved in the development of dementia. I’m working with four different datasets in the DPUK Data Portal and this is enabling me to work with the big numbers which will increase the statistical power of my study, making my results more reliable.

What is the biggest problem that you have faced when working with multiple data sources?

Standardisation is a big challenge for me and my colleagues. When you use multiple datasets you will encounter many different tests, and many different measurements, depending on the study. We need to compare like with like so we have to undertake processes known as ‘data cleaning’. This takes so much of a researcher’s time – and when you are dealing with multiple datasets this data cleaning increases exponentially!

Why is a common data model important for dementia research?

A common data model is a way of mapping all the diverse research data that is collected by many different studies to one common key code. Without it you can’t easily combine or compare datasets, as I’m doing. Scientists need to be able to apply – with confidence – the interpretations of their findings beyond their own data. Carrying out studies using multiple data sources is an integral part of that. It’s not a straightforward task but I see the Data Portal as facilitating the development of a usable common data model for cohort studies.



As scientists, we can’t compare pounds with kilos, for example. Only when we compare like with like can we draw any useful conclusions from our analyses. We need common ways of understanding the richness of data available to us.

BETTER SCIENCE

DPUK allows researchers to conduct studies with bigger numbers, meaning results and analyses are more statistically significant.

OPTIMISING BRAIN IMAGING

The changes in the brain that cause dementia take place 10-15 years before we see any symptoms – a huge challenge for the scientists who are developing and testing treatments.

PET-MR brain imaging is a non-invasive method that gives scientists the opportunity to study these early changes taking place in the brain. The information on brain structures and their activity is critical in finding out whether a particular treatment can slow the degenerative process.



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Image processing can be a significant challenge. We always want to process images in a way that enables us to get the most high-quality data possible, however these steps are not always agreed upon by the scientific community. You can spend a long time figuring out what are the most appropriate steps for your particular dataset. Even simple changes in our methods for processing images can have some quite significant effects on the results of a study. There is definitely a need to think very carefully about image processing in order to produce informative findings.

AMANDA WORKER, A MEMBER OF THE CROSSTALK EXPERIMENTAL MEDICINE STUDY TEAM.
SEE CASE STUDY ON PAGE 34.

Credit: Anna Lukala

BETTER SCIENCE

Scientists need consensus on the best way to process image data. DPUK scientists have developed standardised protocols to follow when working with brain scan data.

GETTING A DETAILED PICTURE OF THE BRAIN'S ACTIVITY

The DPUK Imaging Network equips seven major UK research institutions with '7T' scanners, which enable scientists to collect high-resolution images and obtain much greater detail on the structure and function of the brain. All the scanners are PET-MR, allowing simultaneous collection of complementary types of data.



Heidi Murray-Smith, Research Study Coordinator

IMAGING AMYLOID

Amyloid is a protein that is known to build up in the brains of people who have Alzheimer's disease. It's critical for scientists to be able to understand why and how this protein builds up. PET-MR imaging is one key way of getting this information.

KEY MILESTONES:

- 'Insight 46' study phase 1 complete: 471 participant scans alongside comprehensive medical, neurological and cognitive assessments, including blood sampling for biomarkers and genetics.
- Best practice for image processing procedures developed.

Snapshots from the past: the value of lead-in data

The study members who we have completed PET-MR brain scans for are all members of the MRC National Survey of Health and Development. As one of the oldest British birth cohort studies, it has followed 5,362 individuals since their birth in one week in March 1946. This special group of people – who are all 72 years old – has been followed up since then in 24 waves of data collection. Thanks to the time that these study participants have contributed, we have repeated measurements of many aspects of their health and lifestyle throughout their life. Used together with the brain scans completed earlier this year, we are able to investigate

relationships between health measures in early- and mid-life and subsequent brain health.

The importance of PET-MR

The DPUK network comprises PET-MR scanners, an advanced type of scanner which collects two types of complementary information: high-resolution images of brain structures allowing us to assess subtle changes such as brain shrinkage or mini-strokes; and PET, which allows us to see the presence of amyloid, a protein known to build up in brains affected by Alzheimer's disease. Being able to more accurately determine the location of the amyloid is one way to shed light on how and why it builds up.

BETTER SCIENCE

PET-MR imaging allows scientists to visualise amyloid without expensive and invasive tests. DPUK invested in five PET-MR scanners, allowing scientists to get a better picture of the behaviour of this protein.



DPUK has funded a comprehensive review of the UK brain banks. Cohort participants are interested in brain donation. A full protocol for a pilot programme has been developed with Manchester brain bank.

WIDENING ACCESS TO DATA: IMAGING INFORMATICS

Brain scans are conducted in state-of-the-art facilities up and down the country. DPUK's vision was to make this valuable data much more accessible for the wider research community, beyond only those institutions which collect image data.

The Data Portal's imaging informatics team customised a widely-used neuroimaging research platform, XNAT, to allow cohort studies to upload their image data so that researchers can search and use it.

A HUB AND NODE MODEL FOR BRAIN SCAN DATA

XNAT is an open-source platform allowing image-based research. The DPUK informatics team needed to customise this technology to make it more accessible for the cohort studies which hold image data and the researchers who want to work with it.

THE TEAM BUILT:

- user-friendly functionality for finding brain scan data to work with
- functionality to enable researchers to combine brain scan data that has been released from different cohorts.

Dr Matt South is a Research Software Engineer for the DPUK imaging informatics platform *Credit: Anna Lukala*



There is **200 TB** of space in the imaging central hub to store brain scan data.

Brain scans are typically **1 GB** in size.

Local XNAT nodes currently hold **30** imaging studies, which total **6,000** scans of **4,000** participants.

BETTER SCIENCE

The customised XNAT technology allows Principal Investigators to be able to share their imaging data in a controlled manner through the DPUK Data Portal. Potentially it could allow larger cohorts to be created to increase the power of studies.

BETTER SCIENCE

DPUK's Imaging Informatics Network gives researchers the tools to more easily share their imaging assets. In this way we help them to answer the questions about what data can be legitimately combined and reused, and thus enable larger, more statistically-powerful studies.

ADDRESSING THE IMAGE PROCESSING CHALLENGE

Imaging data is large and complex. Researchers need significant resources to store and process even modest-sized studies and its complexity means that it is hard to judge which results can be legitimately compared.



The logistics of managing large amounts of data for hundreds of MRI-PET scans is complex. Each scan goes through multiple quality control checks that are performed by a highly skilled team. The data must then be processed using computationally-intensive processes to make sure they are suitable for subsequent analyses.

HEIDI MURRAY-SMITH, RESEARCH STUDY COORDINATOR,
MRC NATIONAL SURVEY OF HEALTH AND DEVELOPMENT NEUROIMAGING

DPUK GENETICS

A person's genes – information coded into every cell in the human body – play a vital role in later life health: certain genes may offer protection from degenerative disease while others may indicate greater risk. Genetic data is instrumental in studies of brain disease and scientists need to be able to work with the genetic information collected by cohorts easily and efficiently.

Thanks to the falling costs of a process known as genotyping, more and more cohorts have vast databases of genetic information. However, it is cumbersome and difficult to work with for those without particular expertise and technical resource. DPUK's genetics platform opens up access to this important type of data.

Dr Georgina Menzies at Cardiff University is a bioinformatician – a leading researcher who knows the power of this information in the development of new treatments for dementia.

How do you describe your work?

I work with genetic information and I see my work as discovery: I love to get as much genetic information as possible and try and work out what it means. A person's genes cause the proteins in their cells to fold and interact in complex, highly intricate ways. If we understand the changes that take place in Alzheimer's disease then we can make drugs that target those areas of change.



I'm trying to discover something new, that no one's ever seen before.

What do you and your colleagues do with the genetic information in the blood samples collected by cohorts?

Scientists have known for some time that the genetic variant known as APOE4 is associated with Alzheimer's disease but the story is a lot more complicated than that: my colleagues have identified 27 regions of the human genome that have links with Alzheimer's disease. Combinations of these genes interact

in complex ways. Some combinations are known to show a high risk of developing Alzheimer's disease, and other combinations are protective, indicating low risk. We work with cohorts' genetic data to understand the high-risk combinations and their functional effect (the effect on cells). This will enable drug discovery scientists to target drugs in this area.



Maybe we'll find a genetic variant that is associated with a certain change in the body. It's all about making the small pushes that advance our knowledge of the processes in this disease.

Why is genetic data so valuable?

It's so rich. Even tiny variations in the genetic code can have far-reaching impact on our bodies and our health. Thanks to the work that Valentina has done we have reliable, highly-accurate methods to predict genetic risk of Alzheimer's disease and this allows us – and the wider scientific community – to investigate at fine detail the interaction between nature (genetics) and nurture (eg your environment, upbringing, schooling, early life history) on Alzheimer's disease.



Professor Valentina Escott-Price is an expert in Bioinformatics at Cardiff University.

Valentina leads work on developing new, more accurate ways of predicting risk of developing Alzheimer's disease using genetic data from the GERAD and UK Biobank cohort data.

Taken together, the DPUK cohorts have collected 22 broad types of information, including genetic, imaging and lifestyle data. The DPUK Data Portal gives researchers the technical resources to work with this rich data together.

WHAT IS THE DPUK GENETICS PLATFORM AND WHAT DOES IT MEAN FOR SCIENTISTS?

The idea behind the genetics platform is to allow researchers without bioinformatics expertise to understand the biological effect associated with a particular genetic variant. Through the genetics platform we are making genetics data more accessible, and so facilitating new scientific collaborations, specifically collaborations across disciplines.



A lot of work goes into collecting genetic information and we want as many scientists as possible to be able to use this immensely valuable source of data. The genetics platform enables scientists from different backgrounds to use – and add to – this collective resource.



Dr Brian Tom is Programme Leader at the MRC Biostatistics Unit at the University of Cambridge.

Brian leads work on developing methods of stratifying risk using genetic, imaging and cognitive functioning data found in many DPUK cohorts: CFAS, ELSA, Whitehall II, UK Biobank, CaPS, LBC 1936 and other studies, such as ADNI.

BETTER SCIENCE

Understanding the biological effects of having a particular genetic variant – or combination of variants – gives scientists an insight into the biological processes behind the development of disease. The more genetic information scientists can work with, the bigger the statistical reliability, or power. The DPUK genetics platform gives scientists the resources to conduct genetic studies which are statistically significant.







The lack of volunteers with health data to inform the research is one of the biggest challenges to developing new treatments and preventing dementia.

DR IVAN KOYCHEV, CLINICAL LECTURER IN
OLD AGE PSYCHIATRY AND CLINICIAN SCIENTIST
AT DEMENTIAS PLATFORM UK



Marianne Talbot is a cohort participant who has taken part in DPUK consultations on recruiting to clinical studies.

Credit: Anna Lukala

WHY DPUK IS LAUNCHING *GREAT MINDS*

We know that the causes of dementia start decades before symptoms show, which is why the best people to help study the causes of dementia are healthy volunteers for whom we already have background health information.

This lack of volunteers is a challenge that DPUK is now addressing – we are in the process of recruiting volunteers with health data to share so we can test new interventions, develop new treatments and help prevent dementia before it starts.

The mechanism for recruiting volunteers to research is *Great Minds*. *Great Minds* is a research register working closely with existing health studies (called cohort studies) to recruit volunteers for clinical studies including trials. The power of *Great Minds* is that it brings together the existing data of cohort volunteers with more detailed information that we collect once they have joined the register. The purpose of *Great Minds* is to match these highly characterised volunteers with innovative studies and fast-track dementia research.

Airwave – the police health monitoring study – is the first cohort to join DPUK in the challenge to recruit the best volunteers for dementia studies. In early 2019 DPUK and Airwave are inviting a pilot group from the police cohort to join *Great Minds* and support pioneering trials and experimental medicine. This study will be an end-to-end test of the *Great Minds* pipeline, going from initial contact through detailed assessment, to invitation to join a clinical study. It will be a rigorous test of our procedures and the interest of cohort members to support dementia research in this way.

The generous contribution of *Great Minds*' members will provide a rich pool of well-characterised volunteers that will help accelerate the development of preventative treatments. *Great Minds* members' privacy is strictly guarded and their data are held securely as part of Dementias Platform UK.



The biggest challenge to developing new treatments and preventing dementia is the lack of volunteers with health data to inform the research.

DR IVAN KOYCHEV, LECTURER IN OLD AGE PSYCHIATRY AND DPUK CLINICIAN SCIENTIST

WHY COHORT VOLUNTEERS ARE VALUABLE TO DEMENTIA RESEARCH

THE DEMENTIA STORY



Over the last 20 years there has been a near **100% failure** in the development of new treatments.

THERE IS HOPE

In the last 10 years funding and trials for dementia have doubled, and more and more people are volunteering to take part in trials.



CHANGING THE STORY



To make a breakthrough we need to match the right people to the right trials. We need volunteers who have been part of other health studies.

HOW OUR TRIALS REGISTER FAST-TRACKS TREATMENTS

By joining our trials register, generous volunteers share their data and time to help find a cure for dementia.





HOW GREAT MINDS WILL SUPPORT EXPERIMENTAL MEDICINE

Great Minds enables highly characterised cohort members to be recontacted for dementia-focused experimental medicine

Precision experimental medicine, where specific mechanisms relevant to the start of dementia are studied in detail, is vital for the development of new treatments. To do this we need to study people for whom we already have a lot of background information. *Great Minds* addresses this by enabling individuals from cohorts to volunteer to be recruited to experimental studies, including clinical trials.

Great Minds brings together the existing cohort data which provides background lifestyle and cognitive information, and enhances this with the results from new cognitive, functional and mood assessments. By combining these data researchers are able to better understand the brain health of *Great Minds* members and identify the right volunteers for each study. By enabling highly targeted recruitment, *Great Minds* reduces the risk of expensive trials failures.

Access to *Great Minds* will be controlled through an access committee. Once the committee approves a study, *Great Minds* will select and contact members to provide them with information about the study, and if they agree to participate in the study, they will be given the third party investigators' details.

Cohort members join the *Great Minds* register online, providing information relevant to clinical studies in dementia (including demographics, medical and family history). Since *Great Minds* is optimised for dementia proof-of-concept studies, participants provide new cognitive and mood information by completing web- and smartphone-based cognitive tests every six months. This tracks their brain health and gives up-to-date cognitive trajectories.

Credit: iStock





Highlights from the ELSI report. For more information see www.dementiasplatform.uk/publications

THE COMING OF AGE OF DEMENTIA RESEARCH



Dementia is often characterised as a condition without treatment or hope, yet volunteers from long-term health studies – cohort studies – now offer a key to developing innovative treatments. We brought together **Marianne Talbot**, cohort participant, philosophy lecturer, dementia carer and research champion with **Dr Ivan Koychev**, Lecturer in Old Age Psychiatry and Clinician Scientist at Dementias Platform UK. They discussed the coming of age of dementia research.

MT I follow research into dementia not through choice but necessity. Both my parents died of dementia and for five years I cared for my mother. From my perspective, the speed of research has seemed to be glacial. Yes, I think there have been high points – when David Cameron’s government recognised the need for investment into dementia research – but these have been few and far between.

IK As a clinical scientist I see a real need for progress in dementia research – it is difficult to work with people showing symptoms of dementia where there are few treatments to offer. In the last 10-15 years, there have been great advances – there has been a proliferation of research across neurosciences and brain disorders – and dementia has been the trailblazer. There is now evidence that some treatments are interacting with what we

believe are the causes of the disease – amyloid and tau proteins. The impact of these treatments has been limited because we have only been able to test the treatments on individuals showing clinical symptoms of dementia. We need to test the treatments on individuals who don’t yet exhibit symptoms – we know dementia can start up to 20 years before symptoms show.

MT I understand that I am at a higher risk of developing the dementia because both my parents had the disease, but it doesn’t mean that I will develop dementia. If dementia starts 20 years before the symptoms show, then I may be at that ‘pre-clinical’ stage now. If there are potential treatments that might slow progression of dementia, I would of course consider being tested and involved in trials.

IK

There is evidence that we can change the development of the disease with therapeutic interventions directed at the proteins amyloid and tau. This year a study showed that treatments are reducing symptoms and clearing off the amyloid protein plaques. Our understanding of dementia is moving to where our understanding of cancer is. With tau proteins, we can stage the disease because we can see a spatial pattern of progression.

We need to focus these potential treatments early in the disease process and so we need to be able to identify individuals as early as possible based on their biological data. This will help us understand individual variation in how quickly the disease progresses.

MT

It's exciting to hear about treatments where there is evidence of some impact on individuals and the potential of applying these early in the disease progression. I've been part of cohort studies for a number of years and I will do whatever I can to progress discoveries in dementia. Targeting individual volunteers with new trial treatments to see the value of the intervention gives me real hope.

IK

We've not had the opportunity to test these interventions with volunteers who we know are at a high risk of developing dementia. Using volunteers from cohort studies means that by using existing biological data we can narrow down the people who are at risk of developing symptoms in about 5-10 years and test what impact these interventions have on the path of disease progression.

MT

You need to consider the ethics of unintentionally informing people about their risk of developing dementia if you contact people on the basis of their cohort study data. They may not be aware that their memory test, imaging or genetic data indicates a higher risk – wouldn't it be unethical to contact them if there are no proven treatments?

IK

We considered this risk in detail when setting up *Great Minds* – a register of volunteers willing to be involved in dementia-focused clinical trials. We ask volunteers if they are prepared to be contacted based on the researcher's perception of their risk of developing dementia. Only those consenting to contact will join *Great Minds* and be contacted about potential dementia trials. *Great Minds* promotes well-designed trials that include participants with different risk statuses. This reduces the chance of disclosing to volunteers their level of risk of developing the disease.

MT

This sounds like a decision point for volunteers. They may need time to consider this, but if they do agree, they are giving informed consent. If, like me, volunteers have close family with dementia they probably understand that they are at higher risk of developing the disease – so this disclosure would not be revealing anything new.

IK

With *Great Minds* we're keen to include everyone from a cohort study because we're focused on precision medicine – the impact of an intervention on an individual. People now live with multiple conditions and diseases and we need to be able to treat them and their individual condition. Dementia is not a single disease – the underlying causes will be quite varied, so one treatment may work for one group and not for another.

MT

This sounds much more positive to me than anything I've heard in quite a long time. I've seen drugs failing, but had not understood that sometimes this is because testing on volunteers only takes place late in the progress of the disease – when symptoms show. It gives me great hope that we are now in a position to test these treatments at an earlier stage in the disease when researchers believe they will have greatest impact.



It's exciting to hear about treatments where there is evidence of some impact on individuals, and the potential of applying these early in the disease progression. I've been part of cohort studies for a number of years and I will do whatever I can to progress discoveries in dementia.

MARIANNE TALBOT, LECTURER IN PHILOSOPHY AT THE UNIVERSITY OF OXFORD





RESOURCING
EXPERIMENTAL
MEDICINE

“

We need to understand the risk factors and earlier stages of the disease so that intervention can be provided before the disease really takes hold. Detailed brain imaging is a big part of that.

AMANDA WORKER, PHD CANDIDATE WORKING ON THE DPUK-FUNDED 'CROSSTALK' STUDY

RESOURCING EXPERIMENTAL MEDICINE

DPUK was designed to improve the UK research environment for experimental medicine in dementia, an early stage of drug discovery science in which researchers conduct the first in-human tests. In experimental medicine studies, DPUK scientists are addressing questions of fundamental medical importance, including factors promoting synaptic health and the role of vascular factors in dementia.

DPUK experimental medicine programmes:

1. Vascular disease
2. Synaptic health

IN BRIEF: HOW HAS DPUK IMPROVED THE UK ENVIRONMENT FOR EXPERIMENTAL MEDICINE?

PET-MR scanners in five more UK sites

Scientists are conducting brain scans at much finer detail, enabling close study of amyloid, a known risk factor in the development of dementia. For more, see page 18.

All new scanners have been harmonised so that scans conducted in different sites can be compared accurately. Multicentre studies are now getting started in sites across the country, making participation in research easier for the volunteers around the UK who give their time generously to take part.

Resource transparency

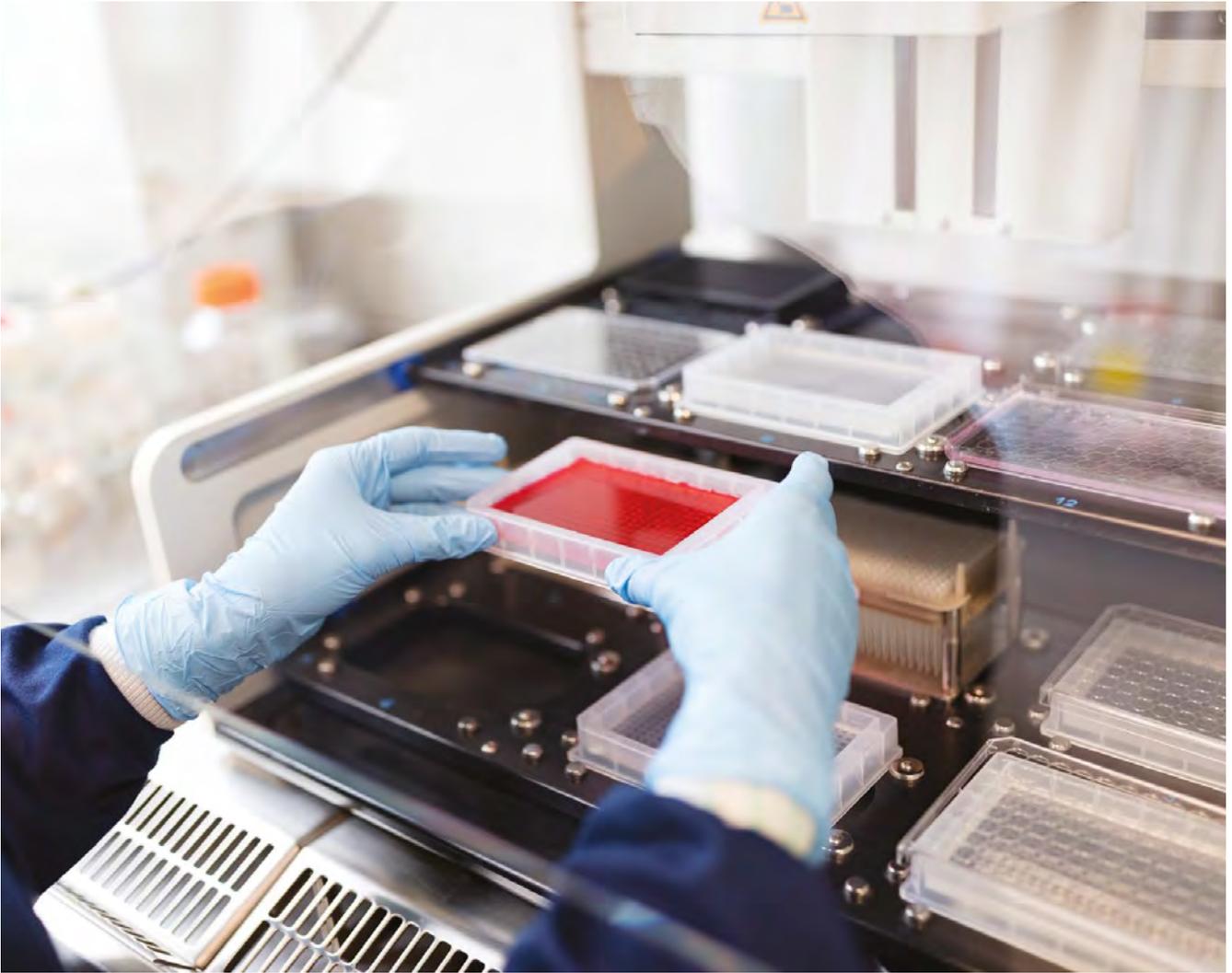
Individual university departments and industry companies have highly specialised expertise in different areas relevant to dementia research. DPUK signposts resources and connects experts with each other.

Industry-standard stem cell processing

UK universities now have the processing power to engage with industry on critical opportunities to better understand dementia at the cellular level. For more, see page 44.

Best practice and standardisation

DPUK teams have developed recommendations for best research practice in a range of areas relevant to dementia: brain banking, cognitive assessment, ethical, legal and social issues, MR-PET scanning, and coding of medical records.



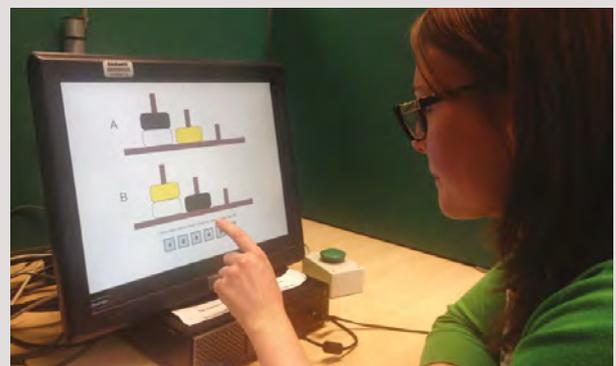
Stem cell processing technology in the DPUK Stem Cells Network Credit: Anna Lukala

WHAT IS EXPERIMENTAL MEDICINE?

Does the drug or technique slow or even stop the development of disease? This is what trials are designed to test, but researchers need to know much more than this when it comes to drug development. Experimental medicine studies happen at an earlier phase in the process. They are designed to test why a drug or compound is producing a particular effect. Involving many different measurements, they are designed to understand which parts of the biological mechanisms cause success or failure.

BETTER SCIENCE

DPUK recommendations on cognitive assessment have improved how mental abilities are measured in UK Biobank. The work was led by John Starr and Ian Deary at the University of Edinburgh.



Cognitive test Credit: Chloe Fawns-Ritchie

LOOKING BEYOND THE BRAIN

Crosstalk is a DPUK-funded experimental medicine study which brings brain and heart image data together. The researchers are aiming to better understand how cardiovascular and brain health are related, particularly in older age.

Amanda Worker is part of the Crosstalk research team. She is one of many DPUK scientists who work with imaging data.



What is your background and your research interests?

My background is in cognitive science and neuroimaging. My current research interests lie in how the body influences the brain and vice versa and how cognitive functions could be affected by the complex dynamic between body and brain. Ultimately, we are trying to understand human functions from a whole system perspective, rather than studying individual organs.



Imaging is an excellent tool to study the brain and I know it will be important in future science too.

What information can we know from a brain scan?

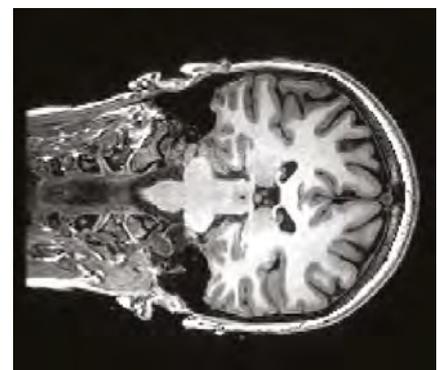
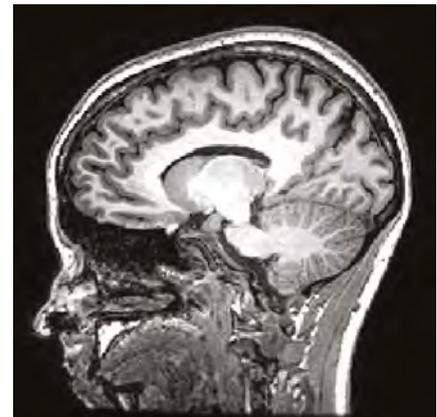
There are two main types of MRI brain scan: structural scans from which we can measure the size and shape of different parts of the brain; and functional scans measuring which parts of the brain become active during specific tasks, or during rest, to see how diseases affect the way the brain activates. Doing both types of scan within a session gives us the most useful information, of course.

What does this mean for dementia?

A significant number of treatment trials have been unsuccessful in the last few years, and this is thought to be the result of intervening too late. We need to understand the risk factors and earlier stages of the disease so that intervention can be provided before the disease really takes hold - and detailed brain imaging is a big part of that. For example, when testing whether a particular treatment may be useful, we can use imaging to see whether an individual shows brain changes that are expected and associated with disease, and whether that treatment is able to slow down or halt the degenerative process.

Why are scans of other organs important?

It is becoming increasingly clear that the function of the brain is affected by other organs and systems – the cardiovascular system, for example. Scans of other organs will arm us with more detailed information about the health of an individual, and will enable us to investigate wider relationships that could offer new insights into brain disease and treatment.



*T1-weighted MRI scans of a healthy brain
Credit: Amanda Worker*

BETTER SCIENCE

DPUK has agreed funding for repeat brain scans of 10,000 participants in the UK Biobank cohort, a figure that vastly outstrips typical repeat-imaging studies. This has enabled further funding for repeat body scans in these individuals.

“

The UK Biobank imaging study is already groundbreaking in the depth and scale of information being collected. Our extension of the study will collect longitudinal imaging data, not only from the brain but will now include reimaging in all body areas. We're doing this on an unprecedented scale. Whole body image data for 10,000 people is an extraordinary level of detail for the scientific community to work with. It will allow us – and the next generations of clinical scientists – to understand the inter-relationships between progressive changes in the brain, body and cardiovascular systems.

PROFESSOR ANDREW BLAMIRE, PROFESSOR OF MR PHYSICS AT THE UNIVERSITY OF NEWCASTLE



OUR EXPERIMENTAL MEDICINE PROGRAMME: SOME EXAMPLES

CROSSTALK: THE IMPACT OF CARDIAC ANATOMY AND FUNCTION ON BRAIN STRUCTURE AND HEALTH

DPUK support

- DPUK cohort (UK Biobank)
- DPUK vascular disease community expertise
- DPUK imaging community expertise

Research question: does heart health impact on brain health?

The researchers reviewed over 22,000 brain scans and compared this to recorded measures of blood pressure. They found that while abnormally high blood pressure (hypertension) is associated with damage to the structure of the brain, it is likely that factors such as inflammation and genetics are also involved. They are now using the scans to complete detailed brain structural measurements, creating a database of new measures which they will share with the original cohort, UK Biobank, for the research community to use.

This study is funded by Dementias Platform UK.

BETTER SCIENCE

Researchers are working with and sharing large imaging datasets. Researchers are deriving new data and, through the imaging platform, will share this data with the original cohort.

GLIAL CELLS AND THEIR ROLE IN ALZHEIMER'S DISEASE

DPUK support

- DPUK infrastructure (PET-MR scanners)
- DPUK imaging community expertise
- DPUK industrial partner involvement (Invicro, GSK)
- DPUK pilot funding facilitated extra investment in the project

Research question: can PET scans provide useful information about astroglial cells?

The degeneration of astroglial cells, important 'helper' cells in the brain, may have a role in the development of Alzheimer's disease. The joint research team (Imperial College London and Invicro) used a range of different imaging techniques to undertake a proof-of-concept study to test if PET scans can provide useful information about astroglial cells. They found that activated astroglial cells are increased in early and established Alzheimer's disease and that the extent of the increase is related to amyloid deposition. Ongoing analyses are exploring how these new measures contribute to better understanding of the early progression of Alzheimer's disease at a time when it could be treated most effectively.

This study received support in-kind from DPUK partners (Imperial College London, Invicro, GSK) who provided resources used in this study.

BETTER SCIENCE

Thanks to DPUK investment in state-of-the-art imaging technology, researchers are able to find new ways to identify Alzheimer's disease at its earliest stages.

RATES, ROUTES AND RISKS TO REDUCE VASCULAR DEMENTIA (THE R4VAD STUDY)

DPUK support

- DPUK vascular disease community expertise
- DPUK pilot funding facilitated extra investment in the project

Research question: what are the rates and risk factors for cognitive impairment after stroke?

Stroke commonly affects cognition, and vascular dementia is the second commonest form of dementia. Fundamental knowledge about risk factors and disease progression is missing, which restricts the prevention, treatment, and effectiveness of patient services. Thanks to DPUK pilot funding and expertise, the R4VaD study will shortly be recruiting a wide range of patients with stroke from across the UK. The R4VaD study will also identify people who are interested in participating in future dementia prevention research.

This study is funded by the Stroke Association, British Heart Foundation and the Alzheimer's Society in addition to Dementias Platform UK.

BETTER SCIENCE

Thanks to vascular expertise facilitated by DPUK and DPUK pilot funding, studies into common causes of dementia are now recruiting larger numbers of participants than ever before. This enables researchers to be more confident in their findings, analyses and recommendations.

TECHNOLOGY SUPPORTING A NEW GENERATION OF STUDIES INTO DEMENTIA

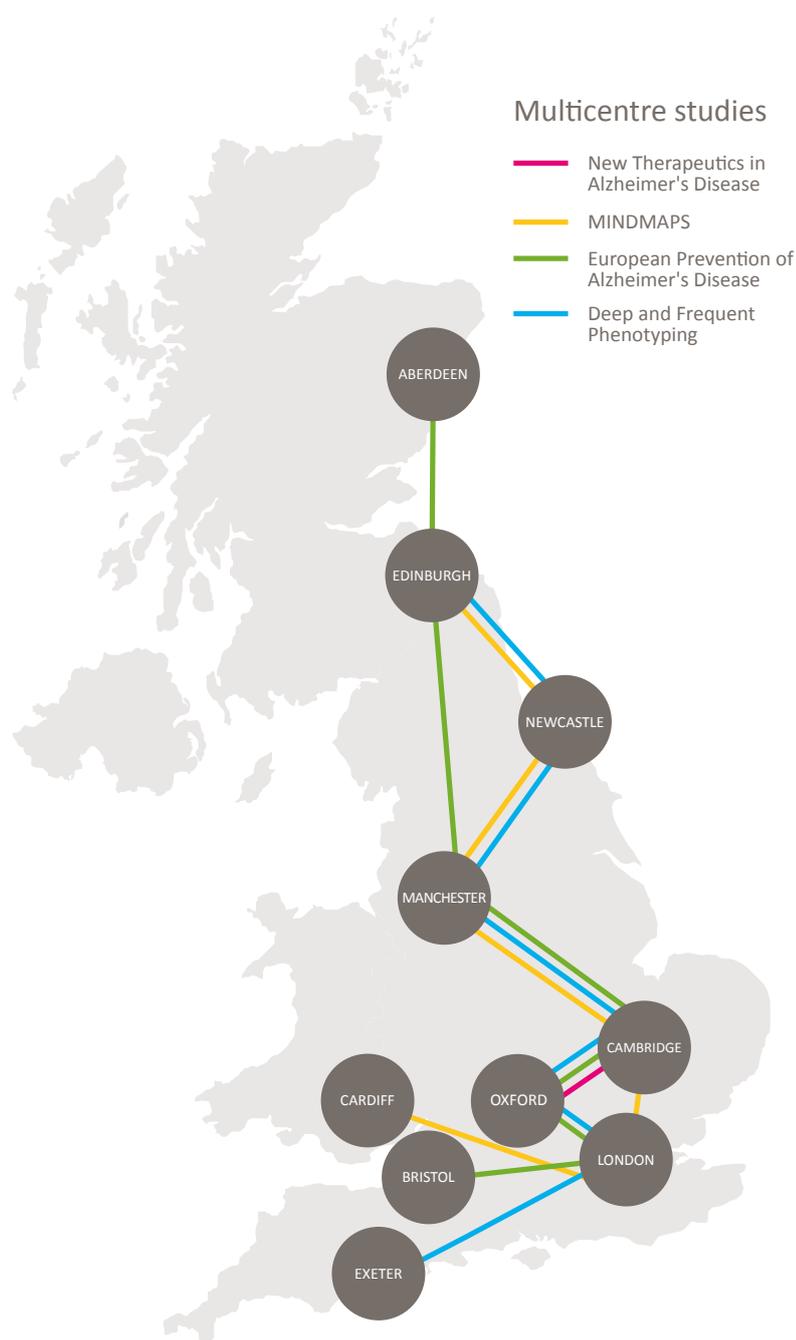
DPUK's technology networks link research institutions across the UK with state-of-the-art infrastructure, supporting a new generation of multicentre experimental medicine studies for dementia.

“

I'm fortunate to live in Oxfordshire so getting to the clinical research facility is quite convenient. It's been great having all my appointments at the same site as visiting busy hospitals can be quite stressful when you don't know the layout. As I work full time the research team have even been able to offer me evening appointments which means I do not have to book time off from work. Not knowing what to expect from being in a clinical trial can cause a little anxiety – especially when I had both an MRI scan and on a separate visit a lumbar puncture – but I was amazed and relieved that all the staff are absolutely brilliant in explaining in detail everything that is going to happen. It is always made clear that your wellbeing is a number one priority for all involved in the clinical trial.

MARY-JANE, PARTICIPANT IN EPAD, A EUROPE-WIDE STUDY NETWORK
PIONEERING THE USE OF ADAPTIVE TRIALS IN ALZHEIMER'S DISEASE





THE IMAGING NETWORK

EDINBURGH
NEWCASTLE
MANCHESTER
CAMBRIDGE
IMPERIAL COLLEGE – INVICRO
KING'S COLLEGE LONDON
UNIVERSITY COLLEGE LONDON

Seven state-of-the-art PET-MR scanners make up the Imaging Network. DPUK teams undertook detailed testing of the scanners to ensure they are calibrated in the same way, so that they can provide reliable results in supporting multicentre studies across the UK. For more, see page 58.

THE STEM CELLS NETWORK

CAMBRIDGE
CARDIFF
EDINBURGH
MANCHESTER
OXFORD
UCL

Examples of the technologies now being used by DPUK scientists:

The **labcyte ECHO** allows scientists to dispense nano-litre volumes of expensive drugs and compounds using acoustic, tipless transfer technology

The **Flexstation** allows scientists to look at cell behaviour by measuring absorbance, fluorescence intensity, fluorescence polarisation and luminescence

The **PherAstar** allows scientists to investigate effects using a powerful and sensitive high-throughput screening plate reader

Automated liquid handling system

iPSC culture lab allows scientists to develop iPSCs (a type of stem cell) for the study of brain cell behaviour.

BETTER SCIENCE

The Stem Cells Network is equipped with industry-standard stem cell processing technology, allowing academic and industry scientists to engage with each other in joint research programmes. This state-of-the-art technology is now being used for experimental medicine studies by researchers in DPUK's partner organisations.

THE FOUNDATION OF UK EXPERIMENTAL MEDICINE RESEARCH

	DESCRIPTION	HOW DPUK ENABLES OR SUPPORTS THIS WORK
DPUK-FUNDED EXPERIMENTAL MEDICINE STUDIES	How do peripheral and central vascular markers relate to cognitive decline?	<ul style="list-style-type: none"> • DPUK cohort (Lothian birth cohort 1936)
	Integration of clinical and cellular phenotypes in the DPUK Deep and Frequent Phenotyping cohort	<ul style="list-style-type: none"> • DPUK cohort (Deep and Frequent Phenotyping) • DPUK infrastructure (Stem Cell Network award) • DPUK stem cell community expertise • DPUK industry partner involvement (SomaLogic)
	Integration of clinical and cellular astroglial activation: multi-modal imaging correlates of astroglial activation, beta amyloid deposition and neuronal activity as markers of cognitive impairment of Alzheimer’s disease	<ul style="list-style-type: none"> • DPUK infrastructure (Imaging Network award) • DPUK imaging community expertise • DPUK industry partner involvement (Invicro, GSK) • DPUK pilot funding facilitated extra investment in the project
	Crosstalk: the impact of cardiac anatomy and function on brain structure and health	<ul style="list-style-type: none"> • DPUK cohort (UK Biobank) • DPUK vascular disease community expertise • DPUK imaging community expertise
	PET imaging changes in cerebral protein synthesis in Alzheimer’s disease	<ul style="list-style-type: none"> • DPUK funding supports 50% of the radiolabel synthesis, scanning cost, metabolite analysis and data acquisition • DPUK infrastructure (Imaging Network award – scanners) • DPUK imaging community expertise
	New Therapeutics in Alzheimer’s Disease (NTAD): MEG biomarker platform development	<ul style="list-style-type: none"> • DPUK industrial partner involvement (Janssen, AZ Medimmune, Lilly) • DPUK infrastructure (Imaging Network award - scanners) • DPUK synaptic health community expertise • DPUK imaging community expertise • DPUK pilot funding facilitated extra investment in the project
	Rates, risks and routes to reduce vascular dementia	<ul style="list-style-type: none"> • DPUK vascular disease community expertise • DPUK pilot funding facilitated extra investment in the project
	Expanding DPUK genetics and integrating with inflammation and immunity research	<ul style="list-style-type: none"> • DPUK cohorts • DPUK Data Portal • DPUK genetics platform • DPUK genetics community expertise
	Deep and Frequent Phenotyping study (DFP)	<ul style="list-style-type: none"> • DPUK cohorts • DPUK industry partner involvement (Cambridge Cognition, Invicro) • DPUK imaging community expertise • DPUK stem cell community expertise

	DESCRIPTION	HOW DPUK ENABLES OR SUPPORTS THIS WORK
DPUK-ENABLED EXPERIMENTAL MEDICINE STUDIES	Molecular Imaging of Neurodegenerative Disease: Mitochondria Associated Proteins and Synapses (MINDMAPS)	<ul style="list-style-type: none"> • DPUK imaging community expertise • DPUK industrial partner involvement (Invicro)
	European Prevention of Alzheimer's Dementia (EPAD)	<ul style="list-style-type: none"> • DPUK Data Portal (cohort matrix) • DPUK cohorts (Brains for Dementia Research, PREVENT, Generation Scotland) • DPUK XNAT imaging portal

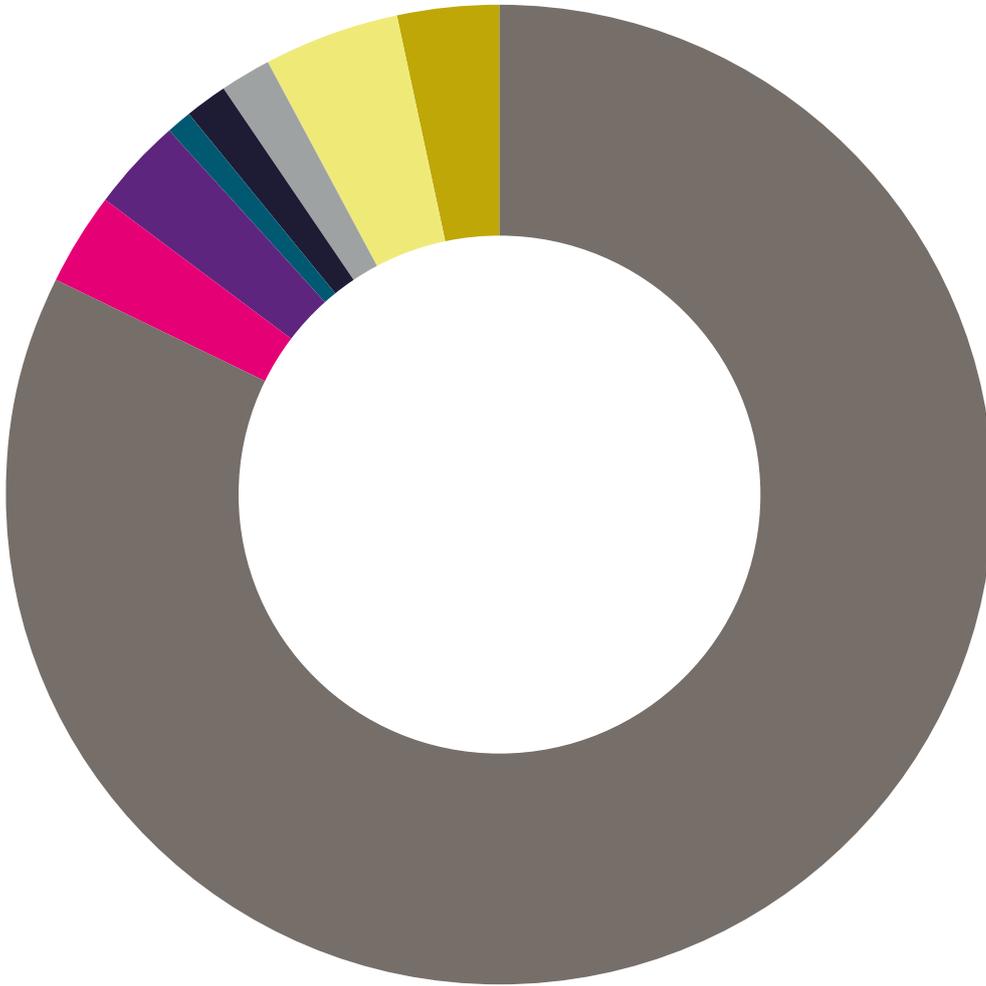


A DPUK-enabled study is a study which uses DPUK infrastructure. We're proud to support such a variety of important science through both our funded and enabled studies.

PROFESSOR JOHN GALLACHER, DPUK DIRECTOR

THE COLLABORATIVE FUNDING MODEL

DPUK's initial investment has leveraged financial and in-kind contributions from industry and research charities.



DPUK's initial investment leveraged significant external funding:

£2,500,000 total funds leveraged from industry and charities for experimental medicine studies

DPUK distributed funding to the following experimental medicine projects:

- £91,000 *Vascular markers in cognitive decline*
- £100,000 *Integration of clinical and cellular phenotypes*
- £21,000 *Multimodal imaging of markers of cognitive impairment*
- £45,895 *Crosstalk: the impact of cardiac anatomy and function on brain structure and health*
- £50,000 *PET imaging of protein synthesis rates*
- £130,000 *New Therapeutics in Alzheimer's Disease (NTAD)*
- £100,000 *Rates, risks and routes to reduce vascular dementia*

THE POWER OF INDUSTRY PARTNERSHIP

DPUK's initial investment has enabled financial and in-kind contributions from industry and research charities.

Dr Iain Chessell heads the neuroscience therapy area in AstraZeneca. As one of the founder industry partners in DPUK, Iain has participated in the Company Partner Forum since DPUK's inception. He shares his perspective on the crux of the problem in Alzheimer's disease and the key outcomes from the DPUK partnership.



NAME: Iain Chessell

POSITION: Head of Neuroscience Therapy Area at AstraZeneca (AZ)



All the diseases that we work on have no cure, and no medicines affect the progression of any of these diseases.

I started working on Alzheimer's disease during my PhD, and seeing patients affected by the disease has motivated me, then and now, to do something about it.

Alzheimer's disease is a long-term illness where symptoms appear decades after initiation and presents the wider drug development community with a particular challenge: symptoms only appear once damaging protein deposits are well established in the brain. We need to intervene at a stage of the disease before these proteins have accumulated to such an extent that their effects cannot be halted. How can we intervene early enough to prevent the deposition in the first place? At the moment this would be very challenging.

Studies in dementia are long and expensive, needing hundreds of patients and at least two years of study; the lack of success so far has meant that a few companies have decided not to continue investing in Alzheimer's disease studies.

DPUK is unique in creating a pre-competitive environment to work on the issues that we, the drug development community, face. DPUK brought me and my counterparts in companies and universities to the table and enabled us to pool our expertise. Together we're coming up with bigger, braver ideas which a single company working in this field wouldn't have pursued working alone.

NTAD is one example of this. It's an exciting and novel experimental medicine (EM) study arising from the Synaptic Health Network that DPUK established. Members of the core group come from AZ, Janssen, Lilly, Cardiff and Cambridge universities. Thanks to examples of collaborative working like this, we're able to develop studies that benefit from specific expertise in particular techniques that different companies offer and, in the future, from cohort resources that might previously have been easily available only to academics.

NTAD will employ magnetoencephalography (MEG) to identify reliable, sensitive and tractable signs of abnormal brain changes that we believe is occurring early in Alzheimer's disease. Our aim is to develop a fit-for-purpose set of biological markers of change ('biomarkers') based around MEG that can be used in next generation EM studies to test novel therapeutic interventions aimed at halting the

progression of Alzheimer's disease. In addition to financial support for NTAD, AZ will provide significant expertise in clinical drug development spanning clinical operations, translational sciences, experimental medicine, biomarkers and biostatistics. We're also benefiting from other partners' expertise in MEG and MEG protocols.

I work with some brilliant people who have vast experience in discovering new potential medicines. We're working to figure out whether they will work in patients, ultimately to make them available as therapies that can be prescribed by doctors. Within the neuroscience group at AstraZeneca, we work extensively with collaborators in academia, and have many PhD students and post-docs in labs all around the world.

We see our colleagues in academia exploring new areas of science, with levels of investment that industry simply can't match. Breaking science often comes from academic research, and partnering and collaborating with the best academic centres in the world gives us the opportunity to turn the fundamental science into life-changing medicines.



Collaboration between industry and academia is critical to success.

REPURPOSING THE DRUG LIBRARIES: THE POWER OF INDUSTRY PARTNERSHIP

The pharmaceutical industry develops thousands of compounds every year, testing their effectiveness in preventing or delaying fundamental disease processes.

DPUK's technology investment is now enabling university scientists to detect potential new uses for these shelved drugs in an innovative partnership with the companies who first developed them.

Facilitated by DPUK, scientists at the University of Oxford are investigating the behaviour of drugs developed by AstraZeneca (AZ) on the cell models derived from DPUK cohorts. They are looking to see if they can be used to target a range of neurodegenerative diseases, including Alzheimer's and Parkinson's diseases.

HOW DID DPUK FACILITATE THIS WORK?

This important work started as a meeting of minds at a scientific conference.

DPUK's Stem Cell Network Lead and the Head of Neuroscience Area Therapy at AZ conceived of the idea to re-examine thousands of AZ compounds through a resource that until now has not been available to industry scientists.

DPUK's investment in state-of-the-art technology helped to secure the partnership. The highly automated technologies now installed at universities in the Stem Cells Network are a significant step up. They are now at a scale to efficiently support collaborations with industry in discovering drugs that have therapeutic implications for neurodegenerative disease.

MAXIMISING THE RESOURCES DEVELOPED IN INDUSTRY

When the tests are successful, the drug is developed, refined and ultimately deployed in a treatment. However, there are many unsuccessful trials and as a consequence, industry companies hold entire libraries of new drugs and compounds that are not tested to their full potential.

THE COLLABORATION IN MORE DETAIL

DPUK enabled universities and industry to pool the best of their resources and realise an under-studied area of drug development science: repurposing compounds stored in industry drug libraries.

The joint team made use of three key resources. An **iPSC stem cell resource** was developed from participant samples in the Lothian birth cohort. Following a process known as 'differentiation', Oxford-based scientists developed patient-specific neurons outside the human body using optimised methods.

Using the **DPUK-funded stem cell technology**, scientists at the University of Oxford are carrying out a range of advanced techniques on these patient-specific living brain cells derived from iPSCs (for more information on iPSCs see page 48). The AZ and university teams are

sharing their analysis and processing techniques with each other as they carry out investigations of hundreds of AZ drugs to see if any have any positive effects.

While AZ contributes **over 4,000 compounds from its drug library** the University of Oxford provides 'disease in a dish' models of neurodegenerative disease. Being derived from samples from the DPUK cohorts makes these cells extremely valuable to the scientists. Researchers are able to test the effectiveness of a wide range of drugs provided by AZ in living cells outside the brain. The DPUK stem cell technology is allowing the team to do this more precisely and on a much bigger scale than ever before possible due to the high throughput, automated screening and imaging equipment now available.



The technology we now have in Oxford vastly improves the efficiency, accuracy and precision of the biochemical testing we carry out here. Now that we are using equivalent technology, it means that industry are willing to engage with the expertise we can offer, and we can pool resources.

DR DEEPAK KUMAR, STEM CELL RESEARCH MANAGER, WADE-MARTINS LAB, UNIVERSITY OF OXFORD



There are thousands of drugs that are currently used for other diseases or have been shown to be safe but not treat the disease they were originally designed for. These drugs offer a fantastic opportunity to find new treatments. We're retesting thousands of drugs with the DPUK stem cell technology to discover target hits to potentially treat neurodegenerative diseases.

DR BRENT RYAN, OPDC CAREER DEVELOPMENT FELLOW, WADE-MARTINS LAB, UNIVERSITY OF OXFORD

OUTCOMES

- Promising findings: a number of early 'target hits' warrant further investigation.
- Closer collaborations: scientists are conducting joint research programmes. Scientists at AZ have shared over 4000 compounds with the Oxford researchers to screen using their iPSC-derived neuronal models. Regular meetings are held where Oxford feeds back results and discussions of suitable thresholds to consider as successful target hits are taken forward.
- Precision and automation: high throughput automated screening and imaging equipment supports large-scale compound screening with precision and efficiency.
- New avenues of study: universities now have the resources to re-test drugs, progressing and testing new ideas.

Credit: Anna Lukala



DRUG DEVELOPMENT: THE COMPLEMENTARY ROLES OF INDUSTRY AND UNIVERSITIES

The development of effective treatment for neurodegenerative disease involves many different stages, from the identification of the undesirable cell-level changes that take place, through to the manufacture of compounds that counter these. Universities and industry play different roles in the process, contributing different knowledge and different resources. Both are needed.

UNIVERSITIES	INDUSTRY
Patient-specific iPSC stem cells reprogrammed from healthy people and those with cognitive decline.	Expertise in storage, handling and preparation of drug and compound solutions.
Expertise and resource to develop patient-specific brain neurons, including: 'disease in a dish' models of neurodegenerative disease, optimised processes and experiments to understand genetic and molecular level changes.	Libraries of thousands of compounds which remain untested beyond their original purpose.
Time resource to follow up on collateral findings and additional effects that are of scientific interest.	Financial resource to investigate the effects of thousands of different compounds on different disease processes.
Equipment, analysis and processing techniques for high-throughput stem cell processing.	Knowledge and background on the implications of compounds and drugs on key molecular pathways in cells.



In brief, using AstraZeneca neuroscience as an example, industry has exquisite focus on delivering medicines to patients. We recognise that investment in fundamental biology is critical to helping the industry community pursue the right targets, but our work starts with drug targets which are usually identified elsewhere – often in academia – and our pursuit of finding drugs for that target is relentless until the target is 'disproven,' usually by our own experimentation. Thus every experiment that we do endeavours to be a decision-making one for the given project that we are working on, and our direction of investment into these projects can change very quickly.

DR IAIN CHESSELL, ASTRAZENECA

PARTNERS IN RESEARCH: THE ROLE OF INDUSTRY IN A MULTICENTRE EXPERIMENTAL MEDICINE STUDY

The Deep and Frequent Phenotyping study (DFP) is the most detailed study into preclinical Alzheimer's disease for its size in the world.

By recruiting 250 people, and carrying out a whole range of different tests with them repeatedly, over the course of one year, researchers hope to pinpoint the elusive early warning signs of Alzheimer's disease. The future success of this grand endeavour relies on the specific expertise that each of DFP's partners in industry brings to the project.

CAMBRIDGE COGNITION: COGNITIVE TESTING

Cambridge Cognition are world leaders in the field of online cognitive assessment software – DFP participants are able to log in and complete highly specialised and sensitive cognitive tests in the way that is most convenient to them. Cambridge Cognition contributes to the management and analysis of these data, which provide detail on many aspects of a person's cognitive ability.

INVICRO: PET IMAGING

PET imaging involves the use of a radioactive tracer which binds to a particular protein, allowing scientists to see where these proteins accumulate inside the brain. It is currently the only way we can observe the development of beta amyloid protein plaques which build up in brains. These are a major characteristic of Alzheimer's disease. As collaborators, Invicro offers PET imaging set-up and analysis in the DFP study.

ASTRAZENECA: STUDY PROTOCOL

AstraZeneca supported the generation of study protocol and set-up for DFP's pilot study and the full study.

NEUROVISION: IMAGING

The build-up of amyloid is a known hallmark of Alzheimer's disease but current methods to accurately measure it are both invasive and expensive. NeuroVision's cameras will be used to image the retina – a very new method with the potential to revolutionise how scientists measure amyloid in the brain.

DATA CURATION

By the end of the DFP study, scientists will have data in a whole range of different areas: MRI, MEG, EEG and PET amyloid brain scans, cognitive tests, gait analysis, eye tests and blood tests. Accordingly, there is significant need for support in the management and curation of all this data. Industry supports these aspects of the study.



DFP is an incredibly important study to help us understand how early disease develops and progresses, and the hope is that the correlation of the endpoint analysis with disease progression will give us real opportunities to choose the 'right' markers to measure disease progress in interventional studies using new medicines. AstraZeneca has been pivotally involved in this DPUK study right from inception, and continues to provide resources for configuring the study into its next phase.

DR IAIN CRESSWELL, ASTRAZENECA

BETTER SCIENCE

Industry companies have highly-developed expertise in specific scientific areas. DPUK brings this distributed expertise together to power the best ideas in dementia research. With experimental medicine studies like DFP employing state-of-the-art methods developed in many different fields, we get ground-breaking research off to the best start.

HOW WILL INDUSTRY BENEFIT FROM THIS COLLABORATION?

Industry needs to test drugs earlier on in the disease process, where there is a greater chance of slowing down or even stopping disease progression. But without knowledge of the early signs of Alzheimer's disease, how can the drug developers test the drugs in the early stages, and know whether the drugs are working? DFP aims to identify these signs – the 'biomarkers' – so that the industry scientists can use biomarkers to recruit the right participants to clinical trials, and test the performance of the compounds they develop.

THE POWER OF DPUK'S NETWORKS: BRINGING TOGETHER THE UK'S EXPERTISE

The UK has a wealth of scientific knowledge and resources for treatments. DPUK transforms these into opportunities for dementia research through its nationwide, partnership approach.

One such opportunity lies in specialist knowledge. Industry companies and university departments have developed specialist expertise in a range of areas of dementia discovery science. To maximise their use in treatment, best practice and resources need to be shared beyond individual departments.

DPUK support for fields such as stem cells, informatics, imaging, cohorts, statistical analysis and genetics helps to develop expert communities far beyond individual universities and companies. It has facilitated the cross-fertilisation of ideas, and the sharing of resources and best practice.

For example, scientists at the University of Oxford have developed highly advanced techniques in stem cell reprogramming. Thanks to the DPUK network, stem cell scientists in many universities and companies are benefiting from an advanced scientific resource.

BETTER SCIENCE

The teams in Edinburgh and Oxford have collaborated to generate stem cells from the blood samples of over 20 different people in the Edinburgh birth cohorts. These are now being shared with sites across the Stem Cells Network. Researchers use them to develop specific brain cells to model the disease development in a dish, and test the effect of different drugs.

INDUCED PLURIPOTENT STEM CELLS (iPSCs): A SHARED RESOURCE

iPSCs allow scientists to create living, patient-specific brain cells and study their behaviour outside the body. These 'disease in a dish' models offer a safe, non-invasive way of researching a difficult-to-access organ.

When a person exhibits symptoms that are characteristic of cognitive decline, such as memory loss and slowness of movement, scientists need to try to understand what is happening on a genetic and cellular level. iPSCs derived from the people who take part in long-term health studies are a uniquely valuable resource.

Starting at the University of Edinburgh: samples from the Lothian birth cohort

Scientists at the University of Edinburgh have been studying the Lothian birth cohorts since 1936. This incredible population study comprises generous volunteers whose cognitive ability and other data have been tracked since childhood. In 2017 the Edinburgh team took blood samples from 24 individuals in order to develop stem cells. Thanks to the existing study of these people, the scientists were able to take samples from three distinct groups: cognitively healthy people; people showing signs of mild cognitive decline; and people showing stronger decline. The samples were first sent to Cedar (a company in the US) for initial reprogramming into stem cells.

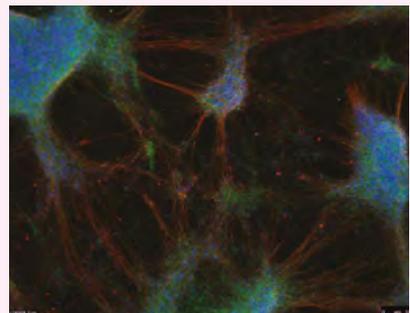
Continuing at the University of Oxford: expanding the stem cell resource

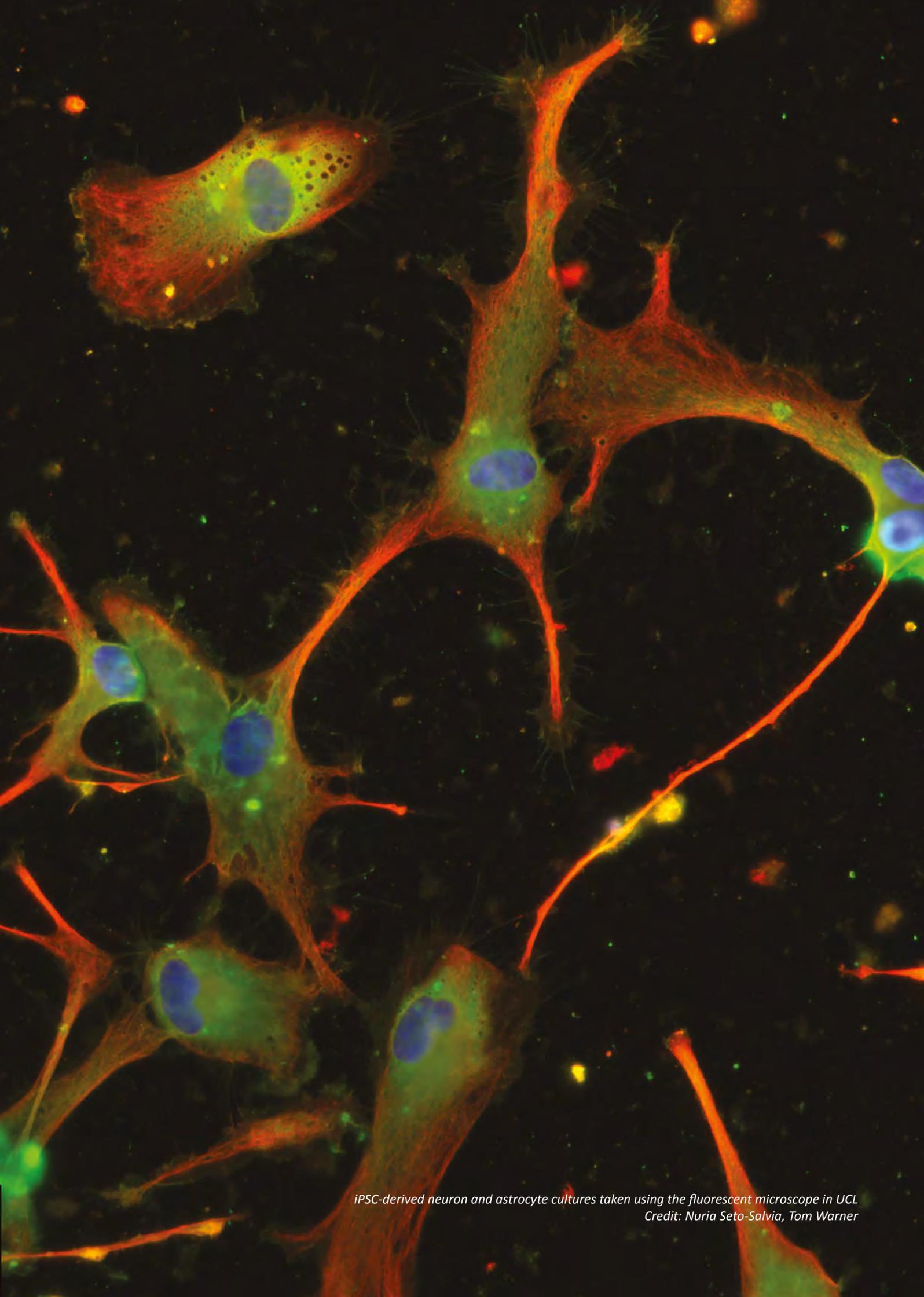
The Edinburgh scientists then shared the Lothian cohort stem cells resource with scientists in Oxford who are working to expand these cells. This process – developing stem cells from blood or skin cells and expanding the sample – is known as 'reprogramming', and is highly complex.

Use at Cardiff, UCL, Cambridge: specialised expertise in particular cell types

Each of the sites in the Stem Cells Network has highly developed expertise in producing different brain cell types from the iPSCs. Individual departments will use the shared patient-specific iPSC stem cells to study the development of key brain cells, including glial cells and dopaminergic neurons. They will compare the characteristics and the behaviour of diseased and non-diseased neurons outside of the brain.

The Oxford team is collaborating closely with industry companies to screen and evaluate the effects of many compounds on iPSC-derived neurons to attempt to discover drugs that could be used in the future to detect earlier, control, or even alleviate neurodegenerative diseases. Read more on page 44.





*iPSC-derived neuron and astrocyte cultures taken using the fluorescent microscope in UCL
Credit: Nuria Seto-Salvia, Tom Warner*

JOINING UP EXPERTS

UK universities and industry have world-class expertise in a range of areas relating to neurodegenerative disease. Thanks to DPUK support for events and scientific travel, the expertise and best practice can be shared.

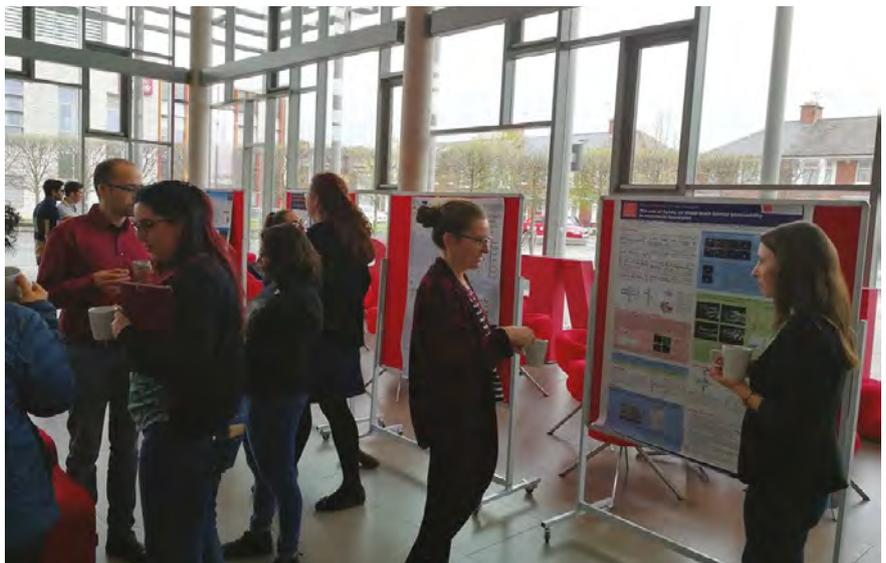
STEM CELLS NETWORK

The DPUK Stem Cells Network meeting takes place annually. Held this year in Cardiff, it took place over two days and was structured into seven key themes, including genetics, transcriptomics, iPSC models of neurodegeneration and the blood brain barrier. Over 90 scientists attended the event.



I got a huge amount out of the day. Discussions were lively on a wide range of very interesting topics. The poster presentation showcased work from nine of my colleagues. It was an opportunity for us not only to communicate our work, but also to network and build future collaborations within the partnership.

DR EMMA COPE, CARDIFF UNIVERSITY



Over 90 stem cell scientists from universities across the UK met thanks to DPUK support
Credit: Dr Emma Cope

NETWORKED EXPERTISE IN THE DPUK STEM CELLS COMMUNITY

- **OXFORD:** reprogramming (developing iPSC stem cells) compound screening, genome editing, dopamine neurons, Parkinson's disease
- **CARDIFF:** genome editing, Huntington's disease
- **EDINBURGH:** cortical neurons, astrocytes, dendrocytes
- **CAMBRIDGE:** cortical neurons, Alzheimer's disease
- **UCL:** Alzheimer's disease
- **MANCHESTER:** blood brain barrier stem cell models

VASCULAR EXPERIMENTAL MEDICINE NETWORK

The DPUK Vascular Experimental Medicine Network targets vascular processes in dementia. The multi-disciplinary team which DPUK brought together includes academic, clinical and industry scientists. The Vascular Experimental Medicine Network benefits from links with other UK and global networks (UK DRI, Cochrane Dementia Group, ISTAART, VasCog). Genuine synergy was achieved through themed scientific meetings including the VasCog conference in London (July 2017) and a two-day DPUK-sponsored workshop in Glasgow on cerebral small vessel disease (Jan 2017).

BETTER SCIENCE

The team has developed best practice to inform future clinical studies and neuropathological assessment of brain vascular disease. See the publication list for more detail.

SYNAPTIC HEALTH NETWORK

There is emerging evidence that a loss of synapses precedes the death of neurons and is a major cause of the early symptoms of Alzheimer's disease.

The DPUK Synaptic Health Network comprises scientists from UK universities and industry: Janssen, Lilly, UCB and AstraZeneca. DPUK supported meetings of this group and allowed them to develop and win additional funding for the New Targets in Alzheimer's Disease (NTAD) study. The study, which got started in April 2018, will measure the electrical activity of the brain using magnetoencephalography (MEG) while participants complete visual recognition tasks. The network is now preparing grant proposals for studies in synaptic PET imaging. This new advanced way of measuring synapse number and function in living people has never been done before.

BETTER SCIENCE

Joint research programmes like NTAD are benefiting from industry expertise in specific methodology, for example MEG scanning.

DPUK SUPPORTS COMMUNITIES OF EXPERTISE IN THESE AREAS:

- Stem cells
- Imaging
- Genetics
- Analytics
- Informatics
- Synaptic health
- Vascular disease
- Cohorts.

DPUK supports research teams to bid for further funding by facilitating planning meetings. The result is that more ambitious studies in dementia get off the ground faster. The synaptic health team won funding for NTAD from DPUK, ARUK, the universities of Oxford and Cambridge, and the industry partners involved in the study – Janssen, Lilly and AstraZeneca.



The imaging network of seven scanners supports UK-wide experimental medicine studies. Credit: Marcus Ginns/Invicro

CONNECTIONS TO BOOST CAREERS

Scientists across our research programmes have access to expertise beyond their own department or company thanks to DPUK networks.



Dr Catherine Calvin leads DPUK's analytics community.



The scale of longitudinal data becoming available through DPUK is a huge opportunity for our field. Our core group is made up of senior analysts and epidemiologists with expertise in dementias research from UK-wide higher education institutions. DPUK funding has supported meetings where we considered the best approaches to take, in terms of harnessing cross-cohort data for more robust evidence, and for capacity building among the UK's analyst community. We developed the idea of a training seminar for Early Career Researchers wishing to exploit the Data Portal and DPUK supported this.



Dr Christian Schnier is an epidemiologist working to understand how scientists can make best use of the data collected by hospitals and GPs – electronic health records – to properly classify people into those with dementia and those without.



For me, the great thing about working with DPUK is that it enables me to work outside the UK Biobank cohort with different cohorts, different electronic health records, and different validation strategies. Last but not least, it's linked me up with experts that I would never have met otherwise.



Sean Denham is an MRI research radiographer. He ensures safe, consistent and high-quality imaging is achieved for any study using DPUK's PET-MR scanners.



DPUK has put me in contact with fellow radiographers across the UK, allowing knowledge exchange among many more researchers from a variety of backgrounds. On the back of working with DPUK, I have been invited to present a lecture about governance in PET-MR, as part of our PET-MR MSc programme.



TRAINING UP THE NEXT GENERATION

Scientists based in big dementia research departments benefit from in-house resources and training opportunities – but the same is not true for those based in smaller units. Furthermore, the insights in dementia may come from non-traditional fields with no prior knowledge of dementia – gamers, probability experts or astronomers, for example.

DPUK is building a community of researchers from many different backgrounds, equipping them with skills and opportunities to work together in new ways to tackle the dementia challenge.

For all researchers, wherever they are based, DPUK provides access to training, development and resources. In the last year, we provided:

- **Next generation seminars:** to facilitate and develop ideas among researchers from across the UK that will lead to new analyses and methods in dementia research
- **Training webinars:** to bring training to researchers around the world, assisting them in accessing the free and powerful Data Portal
- **Networking events:** to build stronger communities of researchers that will share expertise and resources, accelerating their work towards important findings
- **DPUK Discovery Awards:** five awards made to researchers for studies in the Data Portal
- **ECR grants:** supporting the development of Early Career Researchers through targeted funding for pilot studies, collaborative visits, equipment, training courses and support.

NEXT GENERATION SEMINAR: ANALYTICS

Dr Christoph Jindra is an analyst based at the University of Oxford. Along with over 30 other analysts based at different institutions, he travelled to London to attend DPUK's Next Generation Seminar: Analytics.



“I’m a statistician with a background in the social sciences, but health data, and specifically dementia data, is a relatively new context for me to work in. As part of my role I’m working with the ELSA, UK Biobank and Whitehall datasets. I’m aware that DPUK works with these cohorts and I’m always very interested in new statistical methods I could use, so I was keen to go to the seminar to find out more.

“The day included presentations and group sessions. I’m not normally a fan of group work but I will admit that it was valuable to see how the people in my group approached the problem in different ways – sometimes very different ways – due to their different backgrounds.

“For me the best thing about the day was the opportunity to learn about the new statistical approaches that are out there and how we can apply them in cross-cohort analyses. I’ve learnt about new methods which I’ll be able to draw on in future studies. That’s a great outcome for me and means I’ll definitely be on the lookout for other events like this.”



30 analysts from different research backgrounds attended the analysts' seminar
Credit: Jennie Hall

DPUK DISCOVERY AWARDS

The Discovery Awards were grants of up to £50,000 each. They were launched to kick-start promising studies in the Data Portal – and to boost the careers of Early Career Researchers (ECRs) working in dementia research. Every applicant team had to include an ECR.

Following interest from 580 people, awards were made to research teams with expertise in brain imaging, cognitive assessment, vascular disease and early life history – all areas which are critical to the growing scientific understanding of dementia, and how to prevent and treat it.



Four of the five winning teams are led by Early Career Researchers, showing DPUK's commitment to this important aspect of our work. DPUK Discovery Awards were made to:

Dr Chi-Hun Kim, who won an award of £50,000 to investigate the impact of vascular factors on the reported declining incidence of dementia. Chi-Hun leads a collaboration of researchers from the University of Oxford, the University of Edinburgh and the National Institute on Aging in the USA.

Dr Danielle Newby, who won an award of £20,000 to investigate the role of metabolic and cardiovascular disease and treatments in cognitive decline. Danielle will be leading a team of researchers from the University of Oxford and the National Institute of Health in the USA.

Dr Ludovica Griffanti, who won an award of £39,772 to investigate brain imaging data to better understand structural

brain changes that take place in cognitive ageing. Ludovica leads a team of researchers from the University of Oxford.

Dr Tom Booth, who won an award of £37,589 to investigate the reliability of cognitive change in ageing and dementias research. The results may also offer insight into the high failure rate for dementia clinical trials. Tom leads a collaboration of researchers from the universities of Edinburgh and Cambridge.

Dr Sarah Bauermeister, who won an award of £39,500 to investigate childhood adversity and its effect on later conditions, including dementia. Sarah leads a collaboration from the universities of Oxford and Bristol.

“

I'm really excited because this is the first major funding award I have won.

DR DANIELLE NEWBY

*Four of the five DPUK Discovery Awards were awarded to Early Career Researchers
Credit: Paul Tait*

“

Funding attracts funding and I am hopeful that this award will now be the start of a track record of grant success in my research career.

DR SARAH BAUERMEISTER

GRANTS FOR EARLY CAREER RESEARCHERS

Dementias Platform UK has been committed to supporting Early Career Researchers since it started in 2014, through events, workshops, community building and the Discovery Awards. Future generations of dementia researchers will be critical to building a strong, joined up dementia research sector and to finding new treatments. Now, as the project enters its final year, DPUK

has responded to ECRs' requests for small grants to help them overcome some key obstacles they commonly face. Through the ECR grants scheme, DPUK provides up to £5,000 to support pilot studies, collaborative lab visits, equipment, technical support and training courses.



Dr Luke Whiley won a DPUK ECR grant

In its first such grant, DPUK awarded £1,500 to Dr Luke Whiley to learn about 'Molecular Epidemiology of Chronic Disease and the Exposome'. He travelled to Utrecht for the week-long residential training course, paid for by his DPUK grant. Luke is a postdoctoral research associate in the Imperial College London centre of the UK Dementia Research Institute. He reflected on his course as follows:

"Whilst I have strong experience in analytical chemistry and metabolomics, for me to develop my research further I need to learn statistical techniques to tie experimental data to clinical data from large cohorts.

"The course was excellent at describing the suitable statistical methods, using open-source software that will enable me to investigate my data for associations and trends with cognition and dementia.

"Additionally, important networking contacts were made with researchers on the EPIC cohort in the Netherlands, who have access to a longitudinal cohort sample set of interest. This could potentially lead to future important collaborations and would be a significant beneficial outcome of attending the course."

The award itself is also beneficial to Luke's development. For ECRs, success in applying for external funding is an important step as they look to embark on an independent research career.

The outcome for dementia research

Luke will use the new techniques he has learnt to approach data in new ways:



I plan to combine existing metabolomics data from DPUK cohorts, and assess the data in combination with the DPUK Data Portal. Hopefully this will lead to a positive outcome and novel metabolomic discoveries. I hope that this will lead to impactful publications.

OUR SUPPORT FOR EARLY CAREER RESEARCHERS

We awarded **£187k** to ECRs through the DPUK Discovery Awards.

39 ECRs have attended DPUK training events – online and at our conference.

Over the course of DPUK at least **20 ECRs** will have been employed on DPUK-funded programmes of scientific work.

More than 30 ECRs have been involved in DPUK-funded programmes of scientific work to date.

Our ECR grants provide targeted funding to boost ECRs' research independence. The total fund available is **£50k**.



SUPPORTING RESEARCHERS WITH GUIDELINES FROM THE EXPERTS: THE MR-PET COMMUNITY

For us to understand what happens when dementia starts and progresses, we need better insights into an organ that scientists agree we will not fully understand for decades to come. It is also an organ that is very difficult to access: the brain.

Advances in scanning technology, such as combined MR-PET scanners, help us take a look at what happens inside someone’s brain and enable us to learn more. The technology is very new with seven DPUK PET-MR scanners around the UK for researchers to use but which require new knowledge as to the best way to use and interpret images. For example, it is important to know what needs to be standardised between scanners in order to enable researchers to more easily compare findings.

Dementias Platform UK (DPUK) wants to accelerate that learning, and ensure that it is shared with researchers as quickly as possible. The DPUK MR-PET Partnership was created to identify the best way to use MR-PET scanners, and shape a community of researchers who can benefit from that learning and build a unique imaging network for use in large UK-wide clinical studies into dementia.

Understanding exactly how to get the best out of these cutting-edge scanners requires careful study, and the MR-PET team are using an unusual approach to standardising the equipment. Instead of using scanners to test participants, they’re recruiting subjects for scans so that they can ensure that all scanners work to the same standard.

In this harmonisation study, the team will scan 42 healthy elderly volunteers across the seven partner sites around the UK. Each participant will be scanned twice over eight weeks, with the second scan either at the same site or a different site so that the team can compare differences in images of the brain.



It’s the first time we’re using people to test scanners, rather than the other way around.

VIKI RHODES-BRADFORD, RESEARCH PROJECT MANAGER FOR DPUK MR-PET PROJECT

BETTER SCIENCE

RESOURCES FOR RESEARCHERS AND BEYOND

The MR-PET community will provide researchers with:

- **Best practice protocols for imaging**

This will include standard procedures and forms, such as patient information sheets for use in studies, to make research quicker, less burdensome and more harmonised for researchers whilst simultaneously ensuring the highest quality.

- **Training**

The MR-PET partnership will facilitate the access to training resources, both class-room based and online, as well as work shadowing opportunities at different sites, to ensure understanding and sharing of best practice and standardisation.

- **Development of the profession**

This new field of hybrid medical imaging is currently being defined and the skills and expertise of the partnership will contribute to this development.

These resources will be of interest to those working in imaging – particularly those that have experience only in one of the two modalities, as there are fewer experts in the combined fields of MR and PET. This will include MR radiographers, PET technologists, physicists, radiochemists, researchers and professional staff.

As a result, the MR-PET Partnership project will create a new generation of skilled professionals who can interpret these cutting edge scans with accuracy, creating stronger findings and greater insight into the workings of dementia.

CELL ACTIVITY AND DETAILED IMAGES COMBINED IN ONE SCAN

A Positron Emission Tomography (PET) scanner produces detailed, three-dimensional images of how the cells are working inside the body and can be used to help diagnose a number of conditions that affect the normal workings of the brain, such as dementia. It can also be used to help diagnose a range of different cancers and can show how far a cancer has spread or how well it is responding to treatment.

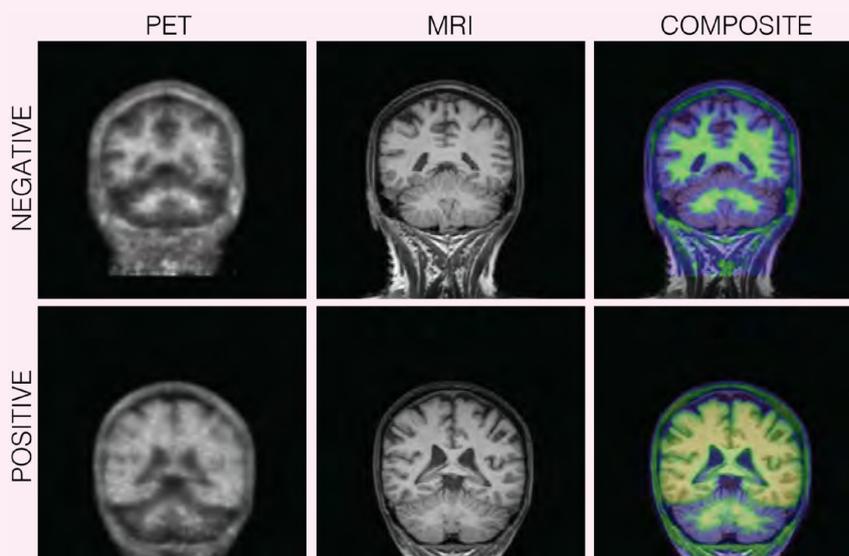
Magnetic Resonance Imaging (MRI) uses strong magnetic fields and radio waves to produce detailed anatomical images of the inside of the body based on the magnetic properties of hydrogen atoms from tissues.

Combining these two different but complementary perspectives of the brain provides researchers with the most complex – and potentially the most informative – map of how dementia develops.

The PET and MR scans are done simultaneously in a PET-MR scanner. This means that while the MR scan is going on, the PET scanner is also collecting information.



GE Signa MR-PET scanner at University of Manchester, one of five new scanners that have been funded by DPUK. Credit: Viki Rhodes-Bradford/ University of Manchester



MR, PET and composite (MR and PET) images of two subjects scanned at University College London Hospital, as part of the MRC Insight 46 cohort study using florbetapir PET radiotracer. Florbetapir binds to amyloid protein, which is found in the brains of Alzheimer patients, so the radiotracer is used as a diagnostic tool. The green/yellow areas in the second set of images correspond to a higher uptake of radiotracer, indicating the presence of amyloid protein, whereas in the first set of images, the blue areas corresponds to no or lower uptake of radiotracer, indicating a normal, healthy brain. Credit: UCL/H as part of the MRC Insight 46 cohort study.

OUR PARTNERSHIPS

The challenges posed by dementia are global in scale. DPUK is one of a growing number of international data-sharing initiatives as research scientists and organisations around the world recognise the value of existing long-term health studies in the development of new treatments.

DPUK's global partnerships take two main forms: as a source of participants for whom we have highly detailed data, and as a big data platform with open-access data and technology for the key research areas in dementia.

OUR PARTNERSHIPS WITH CLINICAL STUDIES

EPAD

EPAD is a unique and ground-breaking European initiative working towards understanding more about Alzheimer's disease and what we can do to prevent and treat it. The project has developed a trial-ready proof-of-concept platform in which new compounds can be tested in a streamlined and efficient way, delivering more effective, targeted interventions that can slow or stop dementia.

Professor Craig Ritchie is the Chief Investigator for EPAD:



DPUK is an important partner to EPAD, accelerating recruitment and screening.

OUR PARTNERSHIPS WITH BIG DATA PLATFORMS

EMIF-AD

EMIF-AD, a leading disease-specific programme, has developed a research platform to ensure research data derived from cohorts of people with Alzheimer's disease is findable, accessible, interoperable and reusable by the research community under appropriate governance and legal requirements. EMIF-AD has been positive towards collaborating, including

sharing source codes and tools with DPUK to develop its own catalogue, and looks forward to a deepening partnership in our mutual fight against this devastating disease.

Professor Simon Lovestone is Co-coordinator of EMIF:



EMIF and DPUK working together offers a unique opportunity for improving access to cohort data in dementia research.

UK BIOBANK

As the world's most detailed cohort, UK Biobank collects its own data. We work with UK Biobank to enhance this extremely valuable resource and optimise its use for dementia research. Tracking brain and body changes against changes in cognitive ability is a key element. We have agreed funding for repeat brain imaging for 10,000 UK Biobank participants. Our cognitive assessment team has developed a new battery of more informative cognitive tests which has been rolled out across the UK Biobank cohort.

Professor Rory Collins is the Director of UK Biobank:



Dementia research based on UK Biobank has benefited substantially from DPUK's guidance.

GAAIN

The Global Alzheimer's Association Interactive Network (GAAIN) is a gateway to providing access to a vast collection of Alzheimer's disease research data, sophisticated analytics tools and computational resources. GAAIN promotes big data sharing among a federated, global network of data partners who are studying Alzheimer's disease and other dementias.

Dr Maria Carrillo is the Chief Science Officer of the Alzheimer's Association, the sponsor for GAAIN:



The mission of GAAIN is to advance a global cooperation of sharing, investigation and discovery. DPUK and GAAIN are working together on the BGC3 project to further expand the reach to develop tools in making dementia data available to researchers from around the globe.

DEMENTIAS PLATFORM KOREA

Dementias Platform Korea (DPK) aims to bring together key East Asian cohorts to improve researchers' ability to work with these. We are working with DPK to create an interoperable network of accessible data for dementia research.

Professor Sang Won Seo is Director of Dementias Platform Korea:



Dementias Platform Korea is delighted to be working with DPUK to establish important links between dementia researchers in the UK and South Korea.

RELATED UK INFRASTRUCTURES

HEALTH DATA RESEARCH UK

Founded in 2017, Health Data Research UK develops and applies cutting-edge data science approaches to clinical, biological, genomic and other multi-dimensional health data to address the most pressing health challenges facing the public. Its mission is to make game-changing improvements in the health of patients and populations through data science research and innovation. We work with Health Data Research UK to assist its vision in developing a UK data commons environment in the UK.

Professor Andrew Morris is the Director of Health Data Research UK:



DPUK is a key partner in developing the wider UK informatics infrastructure. I look forward to Health Data Research UK and DPUK working closely together.

DEMENTIA RESEARCH INSTITUTE

The UK DRI focuses on innovative, early-stage science to advance our understanding of how dementias develop and progress. We work with the UK DRI to provide an environment where UK DRI researchers can develop their insights into the biological mechanisms of diseases: conducting initial in-human studies and working with real-world evidence. UK DRI will interact closely with DPUK to maximise the potential of major patient cohorts and datasets and gain new insights into dementia. This close working will allow the UK DRI to align its research efforts with the most recent clinical insights from studies in human populations into how the different types of dementia develop.

Professor Bart De Strooper is Director of UK DRI:



DPUK provides the next translational step in taking the discoveries of the UK DRI forward to becoming new treatments for dementia.



PERSPECTIVE FROM THE MEDICAL RESEARCH COUNCIL



It is a pleasure to contribute my thoughts to the fourth annual review from DPUK.



MRC leads for UKRI on discovery science to improve human health, and DPUK represents a key strategic investment in our effort to address the immense public health challenge of dementia. Specifically, DPUK was established to capitalise upon the UK's rich heritage of longitudinal cohort data collection and connect the science community to enable more productive and imaginative research on the dementias.



With the establishment of the DPUK Data Portal, we can now scale up dementia research.

The dementias research landscape has changed rapidly over the last five years and DPUK is positioned well alongside the new UK Dementia Research Institute, Health Data Research UK, the NIHR Translational Research Collaboration for Dementia and aligned investments by a range of agencies – this connected landscape is expected to accelerate the pace of translation for the benefit of the many people who live with dementia.

With the establishment of the DPUK Data Portal, we can now scale up dementia research. Scientists from disciplines far wider than those traditionally associated with dementia research are gaining access to the data associated with UK cohorts, have a wider appreciation of what those data have to offer, and can harness the power of combining and integrating datasets to investigate newly discovered associations.

DPUK further allows brain research to be put in the context of the whole body. Through enabling access to a wide array of longitudinal data and triangulation to well-characterised and stratified patient groups, we can begin to unravel how multi-morbidities affect brain disease, as well as pin down the contributions of inflammation, metabolic and vascular factors that have emerged from genetic analyses in the past few years.

DPUK is therefore well poised to support developments at an exciting time for dementias research, with the promise of real progress over the coming years.

Dr Rob Buckle
Chief Science Officer, MRC



DPUK was established to capitalise upon the UK's rich heritage of longitudinal cohort data collection and connect the science community to enable more productive and imaginative research on the dementias.

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Professor Ronan Lyons
Professor Clare Mackay
Professor Paul Matthews
Professor Marcus Richards
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