Biomarkers (DPUK 1000)
Start date: 1 January 2016. **Completion date: Nov 2020**

Overall work package objectives:

To conduct high dimensionality molecular analyses to identify biomarkers for early detection of Alzheimer's disease and related phenotypes.

These objectives to be met through:

1. Construction of three DPUK cohorts, stratified by risk, for biomarker studies to include: 1) cohorts stratified by risk factors and early disease phenotypes; 2) an amyloid cohort, 3) rare genetic variants; complementing work in WP2 (informatics), WP5 (familial risk), and WP14 (Biostatistics).
2. Establishing a DPUK biomarker bio-resource.
3. Data generation.

Deliverables	Milestones	Milestone deadline	Work package dependencies	Person(s) responsible
Objective 1:				
D1.1 Agreement of characteristics of three categories completed	M1.1.1 Protocol generation	M1.1.1 Complete	WP2, WP3, WP4, WP5, WP14	SL, AB KL, CR, PP, JW, SS
	M1.1.2 Protocol published on website; engagement with DPUK community	M1.1.2 Complete		
D1.2 Determination of source of samples from DPUK cohorts	M1.2.1 Use of cohort selection tool / portal to identify cohorts	M1.2.1 Complete		
	M1.2.2 Engagement with cohorts	M1.2.2 Complete		
Objective 2:				
D2.1 Identification of samples meeting agreed criteria	M2.1.1 Use of participant selection tool in portal to identify 1500 participants	M2.1.1 Complete	None	SL (for cohort 1.1 n~1000)
D2.2 Agreement with parent cohorts for individual sample access and analysis	M2.2.1 Agreement with cohorts for protocol to obtain samples for analysis	M2.2.1 Complete	None	SL (for cohort 1.1 n~1000) JS (for cohort 1.2/3 n~500)
D2.3 Transfer of samples to central curation/transfer facility	M2.3.1 Identification of central facility; agreement of process for transfer; transfer and logging samples	M2.3.1 Complete	None	AN
Objective 3:				
D3.1 Agreement for protocols for analysis	M3.1.1 Agreed protocol, contracts, funding and process with partners including SomaLogic, MSD and Araclon	M3.1.1 Complete	None	AN
D3.2 Generation of de novo assays	M3.2.1 Construction of MSD assays for target analyses	M3.2.1 Closed	None	AN
D3.3 Analysis of samples	M3.3.1 Analytic workflows for all modalities	M3.3.1 Complete	Yes	AN
D3.4 Data curation	M3.4.1 Data assembled; data management process agreed; data transfer to analytical teams	M3.4.1 May 20 (was May 2019)	None	AN
D3.5 Data analysis	M3.5.1 Protocols agreed; workflows established; analyses performed; datasets made available to community	M3.5.1 Aug 20 (was Nov 2019)	None	AN

Updates on delivery against milestones since last report

- **M3.2.1 Construction of MSD assays for target analyses (Dec 18)**

  We have not developed the MSD assays for target analyses because of technique issue of the platform. Instead we measured more samples using Somalogic assay.

Now closed

- **M3.3.1 Analytic workflows for all modalities (Feb 19)**

We have developed the analytic workflows for all modalities and applied our algorithm in other data sets. Our algorithm generated good performance in predicting amyloid status which have been published in Alzheimer's & Dementia**.**

- **M3.4.1 Data assembled; data management process agreed; data transfer to analytical teams (May 20 was May 19)**

We have achieved the agreement with SomaLogic. The plasma samples have been shipped to Somalogic Inc based in the US. We will obtain the data in the next couple of weeks. Once the wet-lab work finishes, we will apply the analytic workflows on these data.

- **M3.5.1 Protocols agreed; workflows established; analyses performed; datasets made available to community (Aug 20 was Nov 19)**

Once we obtain the data, we will upload the data to DPUK platform which will be available to the community.

Summary of plan to deliver on outstanding work

We have developed the analytic workflows for all modalities. We will obtain Somalogic data for over 1000 samples in June 2020. Once we get the data, we will apply the analytic workflows on these data and make the data available to the community in August 2020.

Risks	**Mitigation**
1) Neural network might not apply to our data sets because it needs large data input;	1) We will further develop traditional machine learning methods;
2) The wet-lab work might be delayed by SomaLogic.	2) We will negotiate with SomaLogic to prioritize our project.

Team members <u>funded</u> (full or part-time) by DPUK:

Liu Shi

Team members involved with the project but <u>not</u> funded by DPUK: (Now and in the past)

Simon Lovestone, Ajejo Nevado, Alison Baird, Katie Lunnon, Claire Russell, Petra Priotsi, Julie Williams, Steve Smith, Jonathan Schott

Location(s):

University of Oxford

Cardiff University

University College London

Lessons Learnt

First, we learned how to deal with the contract, especially when multiple collaborations are involved. In order to move projects forward, good communication with all collaborators is critical. Second, we learned the importance of having back up plans. For example, in this project, we have not developed the MSD assays for target analyses because of technique issue of the platform. We therefore measured more plasma samples using Somalogic assay.

Please tell us the most successful outcome and what it means to dementia research

We have identified a panel of proteins predict amyloid status with high performance. These proteins could help select the right participants for the right trials, thus having high clinical value. Furthermore, we have found there is causal relationship between amyloid and tau, confirming the central role of amyloid in Alzheimer's.

Outcomes

PUBLICATIONS

Published

- Shi L. et al, 2018, J Alzheimer's Dis, 62, 1181 - 1198

In which we summarised the biomarkers that we have identified and replicated in Alzheimer's disease (AD) patients during the last two decades. Furthermore, we stated the challenges and future direction of AD biomarker development.

- Shi L. et al, 2019 Alzheimer's Dement.

In which we found a panel of proteins predict amyloid status with high performance in both discovery and validation cohort. Furthermore, we found there is causal relationship between amyloid and tau, while the reverse relationship between tau and amyloid was not found.

In review

- Dickkopf-1 overexpression in vitro nominates candidate blood biomarkers relating to Alzheimer's pathology, submitted to J Alzheimer's Dis.

ENGAGEMENT ACTIVITIES

2015

- S Lovestone - Speaker at launch of UK Dementia Platform talk on the NIHR-MRC Dementia Deep and Frequent Phenotyping Feasibility Study 2015

PROTOCOLS

- Discovery study protocol
- Processes in place for targeted biomarker analysis
- Processes in place for untargeted biomarker analysis (SomaLogic)

Project narrative

In this project, we measured over 1200 samples from Generation Scotland study using Somalogic assay which tests over 4000 proteins for each sample simultaneously. This high dimensionality molecular analyses allow us to identify biomarkers for early detection of Alzheimer's disease as well as predicting other related phenotypes. Furthermore, we will share the data within the community so that other researchers will be able to get access to the data set as well.