WP 6

Biomarkers (DPUK 1000)
Start date: 1 January 2016. **Completion date: May 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 (data portal), WP3 (trials readiness), WP4 (amyloid cohort), WP5 (biomarkers), WP14 (biostatistics)	Simon Lovestone, Alison Baird Katie Lunnon, Claire Russell, Petra Priotsi Julie Williams Steve Smith
	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	Simon Lovestone (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	Simon Lovestone (for cohort 1.1 n~1000) Jonathan Schott (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	Ajejo Nevado
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	Ajejo Nevado
D3.2 Generation of de novo assays	M3.2.1 Construction of MSD assays for target analyses	M3.2.1 Dec 2018	None	Ajejo Nevado
D3.3 Analysis of samples	M3.3.1 Analytic workflows for all modalities	M3.3.1 Feb 2019	None	Ajejo Nevado
D3.4 Data curation	M3.4.1 Data assembled; data management process agreed; data transfer to analytical teams	M3.4.1 May 2019	None	Ajejo Nevado
D3.5 Data analysis	M3.5.1 Protocols agreed; workflows established; analyses performed; datasets made available to community	M3.5.1 Nov 2019	None	Ajejo Nevado

Updates on delivery against milestones since last report

- M3.1.1 Agreed protocol, contracts, funding and process with partners including SomaLogic, MSD and Araclon **(Jan 19)**

The contracts and funding has been agreed with SomaLogic in September.

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

The MSD assays for target analyses has not been developed because of technique issue of the platform.

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

Analytic workflows is under construction and the whole workflows will be available once the data set are completely obtained.

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

This task have been delayed because the data has not been generated yet.

Summary of plan to deliver on outstanding work (with dates)

- For M3.2.1, we have not developed the MSD assays for target analyses because of technique issue of the platform. We are planning to use traditional classic ELISA assays or Luminex kits to measure target analyses.
- For M3.3.1, we are developing the analytic workflows for all modalities. We have applied our algorithm using traditional machine learning in other data sets. These methods generated good performance in predicting amyloid status which have been published in Alzheimer's & Dementia. For further development, we will use neural network to develop more advanced methods and workflows.
- For M3.4.1, we have achieved the agreement with SomaLogic. The plasma samples will be shipped in November. Once the wet-lab work finishes, we will apply the analytic workflows on these data.

Risks	**Mitigation**
1) ELISA assays need large plasma volume;	1) We will try to find equivalent Luminex assay to measure target analyses;
2) Neural network might not apply to our data sets because it need large data input;	2) We will further develop traditional machine learning methods;
3) The wet-lab work might be delayed by SomaLogic.	3) 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: n/a

Outcomes

- A review was published in Journal of Alzheimer's disease (Shi L. et al, 2018, J Alzheimers 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.

- A paper was published in Alzheimer's & Dementia (Shi L. et al, 2019 Alzheimers 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.

Project narrative

The objective of this project is to generate multi-modal biomarkers of Alzheimer's disease (AD) which could reflect AD key pathology including amyloid, tau and neurodegeneration. This could help select the participants for clinical trials. Furthermore, we are planning to identify polygenic risk scores from which we will be able to predict the risk of individuals getting Alzheimer's disease.