

Work Package 27a, b & c EM Neuroimmunology

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End date: Dec 2025

Background: There is converging evidence from many sources that the innate immune system plays a key role in the pathogenesis of AD and Dementia with Lewy Bodies (DLB). Early therapeutic studies, including inhibition of microglia by blocking CSF1 receptors in animal studies and phase 2 clinical studies of TNF-alpha blockers, show promise suggesting inflammation may be a key early mechanism to target in dementia. However, there is still a poor understanding of the timing and impact of these inflammatory changes, limiting our ability to determine appropriate biomarkers for subject stratification and as intermediate markers of efficacy for early phase clinical trials. This work package seeks to fill this gap by using large-scale cohort data to examine polygenic inflammatory risk scores as predictors of dementia, combined with a bespoke *in vivo* study of clinical cohorts (using blood and CSF immunoprofiling) to characterize the progression of immune signatures in prodromal and early disease stages.

Aims: To identify inflammatory biomarkers using largescale cohort data and in-vivo data. Specifically, to:

1. Use DPUK cohort data to determine the impact of co-morbidities associated with inflammation and inflammatory pathway specific polygenic risk scores on risk of cognitive decline, MRI changes and development of Alzheimer's disease (AD).
2. Undertake detailed serial immunophenotyping in prodromal and early AD and Dementia with Lewy bodies (DLB) to establish the early immune signature in AD and DLB, determine how this changes over times, and examine the relationship between peripheral and central inflammation.

Work package 27a: Investigation of the impact of polygenic inflammatory pathway risk score and inflammatory comorbidities on onset and progression of cognitive decline and dementia.

Using the DPUK Data Portal to investigate the genetic impact of inflammatory pathway(s) by means of polygenic risk scores and inflammatory comorbidities on onset and progression from cognitive impairment to dementia.

There is still a poor understanding of the timing and impact of innate inflammatory changes along the course of the disease pathway in AD and DLB, yet this is of key importance as at the time dementia presents considerable brain damage has already occurred. Biomarker and brain imaging studies in man concur with animal work in finding inflammation an early feature in AD and DLB; for example, in DLB inflammatory biomarkers in blood and brain normalize in mild dementia is reached (King et al, 2018; Surendranathan et al, 2018), similar to findings in AD, strongly emphasizing the need to study the prodromal stages. By building a cohort of prodromal AD and DLB and undertaking detailed blood and CSF immunoprofiling we will characterize the immune signature at the prodromal stages and, by following subjects over time (3 years) and repeating measurements (at 18 months), we will determine 27a) the immunophenotype in blood and CSF characterizing prodromal AD and DLB; 27b) how immune profile changes over time as diseases progresses to dementia, and 27c) immune profiles

predictive of disease progression. Our work will inform the rational stratification of patients for clinical studies and determine the most effective point(s) of therapeutic intervention. Our study will utilize the DPUK data portal (Knowledge Environment) and latest GWAS information (Kunkle et al, 2018) to examine polygenic inflammatory risk scores as well as inflammatory conditions as predictors of dementia and its prodromes in DPUK cohorts.

We will investigate the hypotheses that i) Inflammatory pathway polygenic risk scores for AD will be one of the key determinants predicting both dementia and associated with it, cognitive decline, and increased rates of whole brain atrophy on serial MR in DPUK cohorts, and ii) Co-morbidities associated with inflammation also predict cognitive decline and increased rates of brain atrophy.

Work package 27b: Peripheral immunoprofiling in people with prodromal and early Alzheimer's disease and Lewy body dementia.

To identify the immune signatures which characterise early Alzheimer's disease and early dementia with Lewy bodies.

Peripheral alterations in inflammatory markers have been described in Alzheimer's disease and in dementia with Lewy bodies. Studies to date suggest these changes occur early in the disease process and may be associated with more rapid clinical decline. However, there are inconsistencies between studies which, to date, have been cross-sectional and have focussed on cytokines and other immune markers, with detailed characterisation of the immunophenotype using deeper phenotyping.

To undertake immunophenotyping and exosome analysis of blood and CSF in new patient cohorts of prodromal Alzheimer's and Lewy body disease and by repeat assessment determine longitudinal changes in immune biomarkers as disease progresses.

Work package 27c: Pilot PET-MR imaging using a novel inflammatory PET ligand.

Several studies have suggested microglial activation in Alzheimer's disease and dementia with Lewy bodies. Studies to date have utilised PET ligands for the translocator protein which are suboptimal as they capture just a part of the inflammatory process, lack sensitivity and/or have binding properties influenced by polymorphisms making them unsuitable biomarkers for 30-50% of people. Recent advances in ligand imaging include developments of putative new targets including the P2X7 and CSF1R receptor.

To undertake a pilot study of inflammatory PET imaging in prodromal AD and DLB using a novel ligand. Ligand receptor development is a rapidly moving field and whilst initially we plan to utilise a ligand for the P2X7 receptor, should new evidence emerge prior to study start, we may choose another ligand.

Objective 1: Investigate the genetic impact of inflammatory pathway(s) on onset and progression from cognitive impairment to dementia. (work package 27a)

Deliverable 1: Identification of appropriate datasets.

Deliverable 2: Obtain data from UK Biobank.

Deliverable 3: Obtain additional datasets.

Deliverable 4: Curate data.

Deliverable 5: Development of a polygenic risk score.

Deliverable 6: Analysis of the genetic impact of inflammatory pathways on disease onset and progression.

Deliverable 7: Obtain and include the DPUK Reimaging subset into the analysis.

Deliverable 8: Identify and obtain additional cohort study datasets and include into the analysis.

Deliverable 9: Complete analysis of the change in biomarkers over time on disease onset and progression.

Deliverable 10: Share results of analysis on the DPUK Data Portal.

Objective 2: DPUK/MRC project reporting (work package 27a)

Deliverable 11: Quarterly reporting

Deliverable 12: Annual reporting

Deliverable 13: Financial reporting

Deliverable 14: End report

Objective 3: Complete study of Peripheral immunoprofiling of people with prodromal and early Alzheimer's disease and Lewy body dementia (work package 27b)

Deliverable 1: Clinical Research Fellows recruited at Cambridge and Imperial.

Deliverable 2: Project set-up.

Deliverable 3: Recruitment of cohort participants with baseline assessment and sampling.

Deliverable 4: Follow-up assessment and sampling.

Deliverable 5: Data Analysis and making data available on DPUK data portal within 6 months of project completion.

Objective 4: DPUK/MRC project reporting (work package 27b)

Deliverable 6: Quarterly reporting

Deliverable 7: Annual reporting

Deliverable 8: Financial reporting

Deliverable 9: End report

Objective 5: Complete pilot study of PET-MR imaging using a novel inflammatory PET ligand (work package 27c)

Deliverable 1: Complete project set-up.

Deliverable 2: Radiochemistry development.

Deliverable 3: Ligand production.

Deliverable 4: Recruitment of participants to study.

Deliverable 5: Perform PET-MR imaging of participants.

Deliverable 6: Complete data analysis of PET-MR scans.

Deliverable 7: Data curation.

Deliverable 8: Curated data available on DPUK data portal within 6 months of project completion.

Objective 6: DPUK/MRC project reporting (work package 27c)

Deliverable 9: Quarterly reporting

Deliverable 10: Annual reporting

Deliverable 11: Financial reporting

Deliverable 12: End report

Objective 1: Investigate the genetic impact of inflammatory pathway(s) on onset and progression from cognitive impairment to dementia.

Milestone	Description	How and who	Outcome	Dates
Deliverable 1: Identification of appropriate datasets				
M1.1.1	Appropriate cohort study datasets identified	Review datasets available (VEP, SB)	Datasets identified	Mar-21
Deliverable 2: Obtain data from UK Biobank				
M1.2.1M	Submit request and receive data from UK Biobank	Apply and receive data (SB, VEP)	UK Biobank data downloaded	Oct-21
Deliverable 3: Obtain additional datasets				
M1.3.1	Submit request and receive data from additional cohort studies	Apply, and receive data (SB, VEP)	Additional datasets downloaded	Jun-21
Deliverable 4: Curate data				
M1.4.1	Curate the datasets received	Curate data (VEP, SB)	Data curated and ready for analysis	Dec-21
Deliverable 5: Development of polygenic risk score				
M1.5.1	Develop a polygenic risk score form the data obtained	Analyse data (VEP, SB)	Data analysed	Dec-21
M1.5.2	Apply the developed score to an initial set of cohorts	Apply scores (VEP, SA)	Participants from initial set of cohorts scored	Jan-22
M1.5.3	Apply the developed score to all selected cohorts	Apply scores (VEP, SB)	Participants from all selected cohorts scored	Oct-22
Deliverable 6: Analysis of the genetic impact of inflammatory pathways on disease onset and progression				

M1.6.1 Analysis of genetic impact of inflammatory pathways using initial set of cohorts	Analyse data (VEP, SB)	Initial cohorts analysed	Oct-22
M1.6.2 Analysis of genetic impact of inflammatory pathways using all selected cohorts	Analyse data (VEP, SB)	All cohorts analysed	Jan-23
Deliverable 7: Obtain and include the DPUK Reimaging subset into the analysis			
M1.7.1 Apply for and obtain the DPUK Reimaging dataset	Apply and receive data (SB, VEP)	Data downloaded	Dec-22
M1.7.2 Analyse the DPUK Reimaging subset	Analyse images (VEP, SB)	1000 images analysed	Mar-23
M1.7.3 Incorporate DPUK Reimaging subset analysis into the genetic impact analysis	Incorporate into wider analysis (VEP, SB)	Analysis completed across combined dataset	Jun-23
Deliverable 8: Identify and obtain additional cohort study datasets and include into the analysis			
M1.8.1 Identify additional appropriate cohort studies to include in analysis	Apply for Data access (SB, VEP)	Additional datasets identified	Mar-23
M1.8.2 Apply for and obtain additional datasets	Include further cohort (VEP, SB)	Additional datasets downloaded	Jun-23
M1.8.3 Incorporate additional datasets into the genetic impact analysis	Include further cohort (VEP)	Analysis completed across combined dataset	Dec-23
Deliverable 9: Complete analysis of the change in biomarkers over time on disease onset and progression			
M1.9.1 Complete analysis across all data sources	Complete analysis (VEP, SB)	Analysis completed	Sep-24
M1.9.2 Write paper for publication on analysis performed	Write paper (VEP, SB)	Paper submitted	Dec-24
Deliverable 10: Share results of analysis on the DPUK Data Portal			
M1.10.1 Share resultant dataset using the DPUK Data Portal	Create and share dataset with DPUK Data Portal (SB)	Resultant dataset available on DPUK Data Portal	Mar-25

Objective 2: DPUK/MRC project reporting				
Milestone	Description	How and who	Outcome	Dates
Deliverable 11: Produce quarterly reports by the required dates				

M2.11.1	Provide Quarterly reports detailing project deliverables and outcomes.	Online quarterly form to be completed for DPUK for MRC meetings	Quarterly report submitted	Mar-21
M2.11.2			Quarterly report submitted	Jun-21
M2.11.3			Quarterly report submitted	Sep-21
M2.11.4			Quarterly report submitted	Mar-22
M2.11.5			Quarterly report submitted	Jun-22
M2.11.6			Quarterly report submitted	Sep-22
M2.11.7			Quarterly report submitted	Mar-23
M2.11.8			Quarterly report submitted	Jun-23
M2.11.9			Quarterly report submitted	Sep-23
M2.11.10			Quarterly report submitted	Mar-24
M2.11.11			Quarterly report submitted	Jun-24
M2.11.12			Quarterly report submitted	Sep-24
M2.11.13			Quarterly report submitted	Mar-25
M2.11.14			Quarterly report submitted	Jun-25
M2.11.15			Quarterly report submitted	Sep-25
Deliverable 12: Produce an annual report by the required dates				
M2.12.1			Annual report submitted	Dec-21

M2.12.2	Annual reports to oversee project status and updates of deliverables and outputs. Information to assess completion criteria as part of payment schedule.	Annual form to be completed for DPUK for MRC meetings. Annual reports submitted to confirm milestone completion for next payment scheduled	Annual report submitted	Dec-22
M2.12.3			Annual report submitted	Dec-23
M2.12.4			Annual report submitted	Dec-24
Deliverable 13: Provide annual financial reporting against the specified budget by the required dates				
M2.13.1	Financial reports submitted at the end of each year. Information to assess completion criteria as part of payment schedule.	Yearly financial statement on spending	Financial report submitted	Dec-21
M2.13.2			Financial report submitted	Dec-22
M2.13.3			Financial report submitted	Dec-23
M2.13.4			Financial report submitted	Dec-24
M2.13.5			Financial report submitted	Dec-25
Deliverable 14: Produce a final work package report by the required date to summarise the work completed and the benefits achieved				
M2.14.1	Final report submitted at end of project.	Lead to complete final report and send to DPUK /MRC for final payment to be made.	Final report submitted	Dec-25

Objective 3: Complete study of Peripheral immunoprofiling of people with prodromal and early Alzheimer’s disease and Lewy body dementia (work package 27b)

Milestone	Description	How and who	Outcome	Dates
Deliverable 1: Staff Recruited (Clinical Research Fellows in Cambridge and Imperial)				
M3.1.1	Advertising process initiated	Clinical Research Fellow posts in Cambridge and Imperial advertised according to university procedures (John O’Brien, Paresh Malhotra and Paul Matthews)	Job Advert	June-21
M3.1.2	Shortlisting process	Review applications and invite shortlisted candidates to interview in Cambridge and Imperial (John O’Brien, Paresh Malhotra and Paul Matthews)	Candidates selected	July -21
M3.1.3	Candidates interviewed and successful candidates offered roles in Cambridge and Imperial	Interviews concluded and references obtained following offer (John O’Brien, Paresh Malhotra and Paul Matthews, HR representatives and other Panel members)	Job offered	July -21

M3.1.4 CRFs complete probationary period and confirmed in post	Clinical Research Fellows undergo relevant University induction and work towards achieving the set probationary objectives (John O'Brien, Paresh Malhotra and Paul Matthews)	2 Clinical Research Fellows in post	Dec-21
Deliverable 2: Project set-up- finalise protocol(s), obtain ethical and HRA approval for project			
M3.2.1 Discuss details and draft relevant documents	Discuss relevant document and produce drafts (John O'Brien, Paresh Malhotra Paul Matthews and CRFs)	Document draft	Jun-21
M3.2.2 Finalise protocol(s)	Write and review project protocols (CRFs, John O'Brien, Paresh Malhotra and Paul Matthews)	Final protocol document	Sep-21
M3.2.3 Apply for ethical and HRA approval	Write, review and submit application(s) for ethical approval (CRFs, John O'Brien, Paresh Malhotra and Paul Matthews)	Approval received	Dec -21
Deliverable 3: Recruitment of cohort participants with baseline assessment and sampling			
M3.3.1 First participant recruited, assessed and sampled	CRFs lead on recruitment and collection of relevant samples (CRFs)	Assessment and samples from first participant	Jan-22
M3.3.2 Half of all participants recruited, assessed and sampled	Identification of 50% subjects completed with relevant samples taken (CRFs)	Assessments and samples from half of participants	Oct-22
M3.3.3 Final participant recruited, assessed and sampled	Identification of final participant completed with relevant samples taken (CRFs)	Remaining participant's assessment and samples completed	Jun-23
Deliverable 4: Follow-up assessment of at least 80% of the original participants with repeat scanning and sampling			
M3.4.1 Follow up of first participant with sampling	Follow up completed (CRFs)	Initial follow up samples collected	Jul-23
M1.4.2 40% of original participants followed up and resampled	At least 40% of participants successfully followed-up (CRFs)	Follow up samples collected from at least 40% of participants	Mar-24
M1.4.3 80% of original participants followed up and resampled	At least 80% of participants successfully followed up (CRFs)	All follow up samples	Dec-24

		collected from at least 80% of participants	
Deliverable 5: Data Analysis and making data available on DPUK data portal within 6 months of project completion			
M3.5.1 Data analysis of baseline samples	Analyses completed and initial results discussed (CRFs, John O'Brien, Paresh Malhotra and Paul Matthews)	Analysis of baseline samples complete	Sept-23
M3.5.2 Data analysis of follow-up samples	Analyses completed and initial results discussed (CRFs, John O'Brien, Paresh Malhotra and Paul Matthews)	Analysis of follow up samples complete	Mar-25
M3.5.3 Data curation	Complete data curation (Research Associate)	Data curation complete	Jul-25
M3.5.4 Making curated data available on DPUK Data Portal within 6 months of completion of data collection	Data available within 6 months of project completion for data requests by DPUK project partners (Research Associate)	Data available	Dec-25

Objective 4: DPUK/MRC project reporting (work package 27b)				
Milestone	Description	How and who	Outcome	Dates
Deliverable 6: Produce quarterly reports by the required dates				
M4.6.1	Provide Quarterly reports detailing project deliverables and outcomes.	Online quarterly form to be completed for DPUK for MRC meetings	Quarterly report submitted	Mar-21
M4.6.2			Quarterly report submitted	Jun-21
M4.6.3			Quarterly report submitted	Sep-21
M4.6.4			Quarterly report submitted	Mar-22
M4.6.5			Quarterly report submitted	Jun-22
M4.6.6			Quarterly report submitted	Sep-22

M4.6.7			Quarterly report submitted	Mar-23
M4.6.8			Quarterly report submitted	Jun-23
M4.6.9			Quarterly report submitted	Sep-23
M4.6.10			Quarterly report submitted	Mar-24
M4.6.11			Quarterly report submitted	Jun-24
M4.6.12			Quarterly report submitted	Sep-24
M4.6.13			Quarterly report submitted	Mar-25
M4.6.14			Quarterly report submitted	Jun-25
M4.6.15			Quarterly report submitted	Sep-25
Deliverable 7: Produce an annual report by the required dates				
M4.7.1	Annual reports to oversee project status and updates of deliverables and outputs. Information to assess completion criteria as part of payment schedule.	Annual form to be completed for DPUK for MRC meetings. Annual reports submitted to confirm milestone completion for next payment scheduled	Annual report submitted	Dec-21
M4.7.2			Annual report submitted	Dec-22
M4.7.3			Annual report submitted	Dec-23
M4.7.4			Annual report submitted	Dec-24
Deliverable 8: Provide annual financial reporting against the specified budget by the required dates				
M4.8.1	Financial reports submitted at the end of each year. Information to assess completion	Yearly financial statement on spending	Financial report submitted	Dec-21
M4.8.2			Financial report submitted	Dec-22

M4.8.3	criteria as part of payment schedule.		Financial report submitted	Dec-23
M4.8.4			Financial report submitted	Dec-24
M4.8.5			Financial report submitted	Dec-25
Deliverable 9: Produce a final work package report by the required date to summarise the work completed and the benefits achieved				
M4.9.1	Final report submitted at end of project.	Lead to complete final report and send to DPUK /MRC for final payment to be made.	Final report submitted	Dec-25

Objective 5: Complete pilot study of PET-MR imaging using a novel inflammatory PET ligand (work package 27c)				
Milestone	Details	How and who	Outcome	Dates
Deliverable 1: Complete project set-up				
M5.1.1	Ligand selection	Final selection of candidate(s) ligands for PET-MR studies (John O'Brien, Franklin Aigbirhio, Paresh Malhotra, Paul Matthews and DPUK2 Neuroimmunology group)	Ligand selected	Oct-21
M5.1.2	Discuss details and draft relevant documents	Discuss relevant document and produce drafts (John O'Brien, Paresh Malhotra, Paul Matthews and CRFs)	Draft document	Mar-22
M5.1.3	Finalise protocol(s)	Write and review project protocols (CRFs, John O'Brien, Paresh Malhotra and Paul Matthews)	Final protocols	May-22
M5.1.4	Apply for ethical and HRA approval	Write, review and submit application(s) for ethical and ARSAC approval (CRFs, John O'Brien, Paresh Malhotra and Paul Matthews)	Application submitted	June-22
Deliverable 2: Radiochemistry development				
M5.2.1	Finalise agreements	Finalise MTA and other agreements needed for ligand production (Contracts team)	MTA and other agreements signed off	Mar-22
M5.2.2	Radiochemistry development	Successfully labelling of chosen ligand with sufficient purity and activity (Radiochemistry development team)	Ligand labelled	Nov-22
Deliverable 3: Ligand production				
M5.3.1	Ligand production	Ligand able to be produced to GMP standards (Radiochemistry production team)	Ligand produced	Feb-23
Deliverable 4: Recruitment of participants				

M5.4.1 Participants recruited to study	Participants selected and accepted onto study	Subjects recruited	Mar-23
Deliverable 5: Perform PET-MR imaging of participants			
M5.5.1 Start in vivo imaging	First subject scanned	First subject scanned	Mar-23
M5.5.2 Halfway in vivo imaging	Half of subjects scanned	Half of subjects scanned	Oct-23
M5.5.3 Finish in vivo imaging	Last subject scanned	Images of last subject	Jun-24
Deliverable 6: Complete data analysis of PET-MR scans			
M5.6.1 Data analysis of PET-MR scans	Analyses completed and initial results discussed (CRFs, John O'Brien, Paresh Malhotra and Paul Matthews)	Data analysis complete	Sep-24
Deliverable 7: Data curation			
M5.7.1 Data curation	Complete data curation (Research Associate)	Data curation complete	Dec-24
Deliverable 8: Data Analysis and making data available on DPUK data portal within 6 months of project completion			
M5.8.1 Making curated data available on DPUK Data Portal within 6 months of completion of data collection	Data available within 6 months of project completion for data requests by DPUK project partners (Research Associate)	Data available on DPUK Data Portal	Jun-25

Objective 2: DPUK/MRC project reporting (work package 27c)				
Milestone	Description	How and who	Outcome	Dates
Deliverable 9: Produce quarterly reports by the required dates				
M6.9.1	Provide Quarterly reports detailing project deliverables and outcomes.	Online quarterly form to be completed for DPUK for MRC meetings	Quarterly report submitted	Mar-21
M6.9.2			Quarterly report submitted	Jun-21

M6.9.3			Quarterly report submitted	Sep-21
M6.9.4			Quarterly report submitted	Mar-22
M6.9.5			Quarterly report submitted	Jun-22
M6.9.6			Quarterly report submitted	Sep-22
M6.9.7			Quarterly report submitted	Mar-23
M6.9.8			Quarterly report submitted	Jun-23
M6.9.9			Quarterly report submitted	Sep-23
M6.9.10			Quarterly report submitted	Mar-24
M6.9.11			Quarterly report submitted	Jun-24
M6.9.12			Quarterly report submitted	Sep-24
M6.9.13			Quarterly report submitted	Mar-25

M6.9.14			Quarterly report submitted	Jun-25
M6.9.15			Quarterly report submitted	Sep-25
Deliverable 10: Produce an annual report by the required dates				
M6.10.1	Annual reports to oversee project status and updates of deliverables and outputs. Information to assess completion criteria as part of payment schedule.	Annual form to be completed for DPUK for MRC meetings. Annual reports submitted to confirm milestone completion for next payment scheduled	Annual report submitted	Dec-21
M6.10.2			Annual report submitted	Dec-22
M6.10.3			Annual report submitted	Dec-23
M6.10.4			Annual report submitted	Dec-24
Deliverable 11: Provide annual financial reporting against the specified budget by the required dates				
M6.11.1	Financial reports submitted at the end of each year. Information to assess completion criteria as part of payment schedule.	Yearly financial statement on spending	Financial report submitted	Dec-21
M6.11.2			Financial report submitted	Dec-22
M6.11.3			Financial report submitted	Dec-23
M6.11.4			Financial report submitted	Dec-24
M6.11.5			Financial report submitted	Dec-25
Deliverable 12: Produce a final work package report by the required date to summarise the work completed and the benefits achieved				

M6.12.1 Final report submitted at end of project.	Lead to complete final report and send to DPUK /MRC for final payment to be made.	Final report submitted	Dec-25
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