WP 26a & b: Synaptic Health

PI/Leads: James Rowe, Cambridge - academic lead; John Isaac, J&J - industry lead

Start date: 1 Jan 2021 **End Date:** 31Dec 2025

Objective of the project: This work package is split into two streams; (WP26a) addresses the correlation of key pre-synaptic markers to synaptic health. Namely to assess whether the synaptic vesicle glycoprotein 2A (SV2A, detected by PET ligand) in participants with amyloid positive symptomatic AD correlates with clinical decline. In addition, assess whether cerebrospinal fluid (CSF) synaptic degradation products reflect synaptic loss on imaging and whether synaptic density has a role in its physiological function in humans. The (WP26b) stream focuses on assessing whether post-synaptic levels of the transmembrane *AMPA* receptor regulatory protein (TARP γ8 AMPAR) are reduced in early AD and if this change correlates with memory impairments.

Background: Synaptic loss and altered synaptic plasticity occurs in early Alzheimer's Disease (AD) and other degenerative dementias. Dysfunction of the synapses precedes phenotypic manifestations, and later correlates strongly with cognitive impairment in AD and other tauopathies. For quantitative *in vivo* assays of human synaptic pathophysiology in future trials, this work will introduce and/or validate a new set of tools related to synaptic density and function.
Preliminary human studies in DPUK and elsewhere confirm reduced UCB-J binding in AD and mild cognitive impairment (MCI). Synaptic health biomarkers may facilitate disease progression monitoring in Ph1b/2a studies, with more direct mechanistic relevance and sensitivity than commonly used late biomarkers (e.g. atrophy). To evaluate the trial-readiness study of presynaptic changes, longitudinal "phase 0" studies are required. There is also a pressing need for post-synaptic markers. The EM Incubator will evaluate the first-of-its-kind TARP γ8 AMPAR PET ligand for human use (transmembrane AMPA receptor regulatory protein γ8 AMPA receptor ligand [18F]JNJ-64511070), developed by DPUK partner Janssen. Preclinical and unpublished human data have been made available to DPUK, in developing the plans for its assessment in people with Alzheimer's disease. The high density of postsynaptic binding to hippocampal glutamatergic synapses is especially useful in the context of AD.

Aim: To determine the functional relevance of changes in pre-synaptic and post-synaptic density, plasticity and function, in people with – or at risk of – dementia. These changes will be assessed in relation to preclinical models, and used to optimise clinical trials.

Team: James B Rowe (JBR, Cambridge, co-lead), Haddy KS Fye [HKSF, DPUK II Project Manager) John Isaac (JI, Janssen, co-lead), Mark Woolrich (MW, Oxford), Franklin Aigbirhio (FIA, Cambridge), Ilan Rabiner (IR, KCL/Invicro), Nick Allen (NA, Cardiff), Andy Randall (AR, Exeter), Kei Cho (KC, KCL, also DRI investigator), Stephen Lowe (SL, Lilly), Darrel Pemberton (DP, Janssen), Michael Perkinton (MP, AZ), Joel Mercier (JM, UCB), Martin Gunthorpe (MG, Autifony), Magnus Ivarsson (MI, Rodin Therapeutics), Ece Kocagoncu (EK, Cambridge), Post Doctoral Research Associate (PDRA)-position to be filled.

Objective 1: Determine the correlation of key pre-synaptic markers to synaptic health (baseline) (work package 26a)
Deliverable 1: Recruitment of teams and key personnel.
Deliverable 2: Site set-up and protocol approval for full work package.
Deliverable 3: Identify ready to test markers for assessing pre/post-synaptic pathophysiology.
Deliverable 4: Baseline execution.
Deliverable 5: Participant engagement to ensure retention.
Deliverable 6: Follow up execution.
Objective 2: Assess whether post-synaptic levels of TARP γ8 AMPAR are reduced in early AD and if this correlates with memory impairment (work package 26b)
Deliverable 7: Recruitment of teams and key personnel.
Deliverable 8: Site set-up and protocol approval for full work package.
Deliverable 9: Sub-study project execution.
Deliverable 10: Identify ready to test markers for assessing pre/post-synaptic pathophysiology.
Deliverable 11: Data analysis and dissemination.
Objective 3: DPUK/MRC Reporting
Deliverable 12: Produce quarterly reports by the required dates.
Deliverable 13: Produce an annual report by the required dates.
Deliverable 14: Provide annual financial reporting against the specified budget by the required dates
Deliverable 15: Produce a final work package report by the required date to summarise the work completed and the benefits achieved

Objective 1: Determine the correlation of key pre-synaptic markers to synaptic health (work package 26a)				
Milestone	**Description**	**How and who**	**Outcome**	**Dates**
Deliverable 1: Recruitment of teams and key personnel				
M.1.1.1	DPUK2 Experimental Incubator Project Manager role advertised and filled.	Job description developed, Interviews performed and candidate offered position. (JBR)	Project Manager role filled.	Mar-21
M1.1.2	Post-Doctoral Research Associate (PDRA) role advertised.	Job description finalized and advertised by University HR. (HKSF, JBR)	Position advertised	Jun-21

M1.1.3	PDRA role shortlisting, interview and offer.	Review candidate, invite for interviews, and offer made to suitable candidate. (HKSF, JBR)	Post-doctoral role filled.	Aug-21
M1.1.4	PDRA appointed and in post.	Offer accepted and pre-employment checks completed. (HKSF, JBR)	PDRA start.	Oct-21
Deliverable 2: Site set-up and protocol approval for full work package				
M1.2.1	Finalise recruitment sites and named key personnel to be involved.	Determine appropriate sites and identify key personnel. (JBR, PDRA, HKSF, MW)	Sites and personnel finalized.	Oct-21
M1.2.2	Undergo site registration process and development of key documentation.	Liaise with site review boards regarding SHINE protocol. (JBR, HKSF, PDRA)	Study protocol under review.	Jul-21
M1.2.3	Site Investigators to approve final protocol.	SHINE protocol approved. (MW, JBR)	Site approval of study protocol.	Aug-21
M1.2.4	Submit simultaneously to institutional ethical and oversight approval.	Liaise with ethical review boards regarding SHINE protocol. (HKSF, EK, JBR, MW)	Protocol under ethics review.	Aug-21
M1.2.5	Completion of all approval and regulatory signatures.	Sites ready to apply full protocol. (JBR, MW, HKSF, PDRA)	Green light for recruitment commencement.	Dec-21
Deliverable 3: Identify ready to test markers for assessing pre-synaptic pathophysiology				
M1.3.1	Ensure access for test sites to novel markers/ligands.	Pharmaceutical partners to approve ligand supply to testing sites. (EK, JI, MW, JBR)	Confirms readiness of all experimental markers.	Aug-21
M1.3.2	Ensure access to infrastructure and equipment for testing.	Identify and execute pilot procedures required for approved start. (JBR, MW, EK)	Testing equipment ready for commencement.	Aug-21
Deliverable 4: Baseline execution				
M1.4.1	First baseline participant recruited.	First participant consented, assessed and sampled. (PDRA, MW, JBR)	Active participant enrolment started.	Jan-22
M1.4.2	50% Target participants recruited.	Recruitment checkpoint, opportunity to make amendments. (PDRA, MW, JBR)	Check recruitment is on track.	Jun-22
M1.4.3	100% recruitment target completed.	Target participants reached in Oxford and Cambridge. (PDRA, MW, JBR)	Participant enrolment completed.	Nov-22

M1.4.4	Create data reporting platform / liaise with Data Portal team to allow compliant submission.	Develop/set-up data reporting platform to deposit complete study data. (JBR, PDRA)	Upload baseline participant data.	Jan-22
M1.4.5	Dissemination of baseline data via DPUK data portal.	Convert data into meaningful results for dissemination. (PDRA)	Data available for review, analysis and hypothesis generation.	Jul-23
Deliverable 5: Participant engagement to ensure retention				
M.1.5.1	Mid-point contact participants to encourage retention and aid follow up.	Mailshot, phone-calls and check-in's at mid-point of study. (PDRA, HKSF, JBR, MW)	Encourage retention and facilitates continued interest.	Jun-23
Deliverable 6: Follow up execution				
M1.6.1	Follow up participants invited and assessed.	Follow up contact and assessments made. (PDRA, HKSF, MW, JBR)	Participants available for follow up visit identified & invited.	Jan-23
M1.6.2	80% Target follow up reached.	Check against baseline to assess if target reached. (PDRA, MW, JBR)	Follow up rate determined.	Nov-23
M1.6.3	Follow up mop up and completion.	If 80% not reached, additional exercise to boost follow up rate. (PDRA, HKSF, MW, JBR)	80% Follow up target reached.	Apr-24
M1.6.4	Data curation.	Update data reporting platform with follow up time-point. (PDRA, MW, JBR)	Upload participant follow up data.	Aug-24
M1.6.5	Dissemination via DPUK data portal.	Update reports to include follow up data and results. (PDRA, MW, JBR)	Full study data available for analysis, review and hypothesis generation.	Dec-24

Objective 2: Assess whether post-synaptic levels of TARP γ8 AMPAR are reduced in early AD and if this correlates with memory impairment (work package 26b)				
Milestone	**Description**	**How and who**	**Outcome**	**Dates**
Deliverable 7: Recruitment of teams and key personnel				
M2.7.1	Post-Doctoral scientist role advertised and filled	See milestone 1.1.4	See milestone 1.1.4	Oct-21

Deliverable 8: Site set-up and protocol approval for full work package				
M2.8.1	Process of protocol and ethical approval for post-synaptic package.	See milestones 1.2.1-1.2.5. (JBR, PDRA, HKSF, MW)	Set up finalized, green light to recruit.	Dec-21
Deliverable 9: Sub-study project execution				
M2.9.1	First baseline participant recruited.	First participant consented, assessed and sampled. (PDRA, MW, JBR)	Active participant enrolment started.	Apr-22
M2.9.2	50% Target participants recruited.	Recruitment checkpoint, opportunity to make amendments. (PDRA, MW, JBR)	Check recruitment is on track.	Jun-22
M2.9.3	100% recruitment target completed.	Target participants reached in Oxford and Cambridge. (PDRA, MW, JBR)	Participant enrolment completed.	Sep-22
M2.9.4	Create data reporting platform / liaise with Data Portal team to allow compliant submission.	Develop/set-up data reporting platform to deposit complete study data. (JBR, PDRA)	Upload baseline participant data.	Jan-22
M2.9.5	Dissemination of baseline data via DPUK data portal.	Convert data into meaningful results for dissemination. (PDRA)	Data available for review, analysis and hypothesis generation.	Jul-23
Deliverable 10: Identify ready to test markers for assessing post-synaptic pathophysiology				
M2.10.1	Access and pilot radiochemistry for the novel markers/ligands (e.g. Janssen ligand for TARP γ8 AMPAR).	Synthesis protocol implementation (PDRA, JI, MW, JBR, FIA, IR)	Confirms readiness of all experimental markers	Dec-21
M2.10.2	Update ethics and protocol to ensure permissions for novel ligand.	Submission to relevant boards. (Site leads, PDRA)	Protocol accepted, green light for use.	Mar-22
Deliverable 11: Data analysis and dissemination				
M2.11.1	Data deposit and curation.	Identify/set up data management platform and deposit baseline data. (PDRA, MW, JBR)	Upload baseline participant data.	Jan-22
M2.11.2	Dissemination of baseline data via DPUK data portal.	Convert data into meaningful results for dissemination. (PDRA)	Data available for review, analysis and hypothesis generation.	Dec-22

Objective 3: DPUK/MRC project reporting				
Milestone	**Description**	**How and who**	**Outcome**	**Dates**

Deliverable 12: Produce quarterly reports by the required dates				
M3.12.1	Provide Quarterly reports detailing project deliverables and outcomes.	Online quarterly form to be completed for DPUK for MRC meetings	Quarterly report submitted	Mar-21
M3.12.2			Quarterly report submitted	Jun-21
M3.12.3			Quarterly report submitted	Sep-21
M3.12.4			Quarterly report submitted	Mar-22
M3.12.5			Quarterly report submitted	Jun-22
M3.12.6			Quarterly report submitted	Sep-22
M3.12.7			Quarterly report submitted	Mar-23
M3.12.8			Quarterly report submitted	Jun-23
M3.12.9			Quarterly report submitted	Sep-23
M3.12.10			Quarterly report submitted	Mar-24
M3.12.11			Quarterly report submitted	Jun-24
M3.12.12			Quarterly report submitted	Sep-24
M3.12.13			Quarterly report submitted	Mar-25
M3.12.14			Quarterly report submitted	Jun-25
M3.12.15			Quarterly report submitted	Sep-25
Deliverable 13: Produce an annual report by the required dates				

M3.13.1	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
M3.13.2			Annual report submitted	Dec-22
M3.13.3			Annual report submitted	Dec-23
M3.13.4			Annual report submitted	Dec-24
Deliverable 14: Provide annual financial reporting against the specified budget by the required dates				
M3.14.1	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
M3.14.2			Financial report submitted	Dec-22
M3.14.3			Financial report submitted	Dec-23
M3.14.4			Financial report submitted	Dec-24
M3.14.5			Financial report submitted	Dec-25
Deliverable 15: Produce a final work package report by the required date to summarise the work completed and the benefits achieved				
M3.15.1	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