MSCA POSTDOCTORAL FELLOWSHIP

Horizon Europe - Marie Sklodowska-Curie Actions

Astrocyte-Neuron Metabolic Coupling in Neurodegeneration

NEUROGLIA-PF

Field	Value
Fellowship Type	European
Call Identifier	HORIZON-MSCA-2026-PF-01
Duration	24 months
Researcher	Experienced Researcher (to be named in Part A)
Host Organisation	Karolinska Institutet, Sweden
Supervisor	Prof. Lindqvist
Research Field	Life Sciences (LIF) - Neuroscience / Neurodegeneration

Abstract

NEUROGLIA-PF investigates the failure of the astrocyte-neuron lactate shuttle (ANLS) in the early stages of Alzheimer's disease (AD) and tests whether restoring astrocytic lactate export can rescue synaptic function in AD mouse models. Astrocytes fuel neurons through the ANLS, but how and when this metabolic coupling breaks down in AD remains unknown at cellular resolution. Using a novel combination of longitudinal two-photon in vivo imaging with genetically encoded FRET-based metabolic biosensors and LC-MS/MS metabolomics, the experienced researcher will map ANLS disruption from pre-plaque stages through early pathology in 5xFAD and APP/PS1 mice, produce the first quantitative in vivo atlas of glial metabolic failure in AD, and test MCT4-mediated metabolic rescue as a new therapeutic strategy. Hosted at Karolinska Institutet under the supervision of Prof. Lindqvist, a world-leading expert in astrocyte metabolism and two-photon imaging, the fellow will acquire advanced interdisciplinary skills in optical neurophysiology, metabolomics, and AAV-based gene delivery, building a uniquely competitive research profile for an independent academic or translational career. All data will be shared openly under FAIR principles, and results will be disseminated to scientific, clinical, and public audiences. NEUROGLIA-PF opens a new metabolic angle on AD pathogenesis with direct therapeutic relevance, contributing to the urgent societal challenge of developing disease-modifying treatments for neurodegeneration.

Keywords: Alzheimer's disease, astrocyte-neuron lactate shuttle, two-photon imaging, metabolomics, glial metabolism, MCT4, neurodegeneration, FRET biosensors, synaptic plasticity, open science

PART B1

SECTION 1 - EXCELLENCE

1.1 Quality and Pertinence of the Research Objectives

Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder globally, affecting over 55 million people and projected to triple in incidence by 2050. Despite decades of research, disease-modifying therapies remain elusive, largely because the field has focused on neuronal pathology while overlooking the critical supportive and metabolic roles of astrocytes. Astrocytes are the principal cellular mediators of the astrocyte-neuron lactate shuttle (ANLS), a mechanism by which astrocytes convert glucose to lactate via aerobic glycolysis and export it to neurons as a preferred oxidative fuel. Disruption of this shuttle has been implicated in synaptic failure and early cognitive decline, yet the precise spatiotemporal dynamics of ANLS breakdown in the preclinical stages of AD remain entirely unmapped at cellular resolution in living brain tissue.

NEUROGLIA-PF advances decisively beyond the current state of the art by combining, for the first time, longitudinal two-photon in vivo imaging with genetically encoded metabolic biosensors (Laconic, iNap, Perceval-HR) and targeted mass-spectrometry-based metabolomics to produce a quantitative, cell-type-resolved atlas of astrocytic lactate and energy metabolite dynamics in early-stage AD mouse models (5xFAD and APP/PS1). The project pursues four specific, measurable research objectives: (RO1) to characterise the baseline spatiotemporal profile of astrocytic lactate export and neuronal lactate uptake in wild-type mice using chronic two-photon imaging through cranial windows by Month 9; (RO2) to map the progressive disruption of ANLS stoichiometry from pre-plaque stages through early plaque deposition in AD models at single-cell resolution by Month 16; (RO3) to identify the metabolomic signature of ANLS failure in hippocampal and cortical tissue using untargeted and targeted LC-MS/MS metabolomics by Month 20; and (RO4) to test whether pharmacological or genetic enhancement of astrocytic monocarboxylate transporter 4 (MCT4) activity can restore neuronal lactate supply and rescue synaptic plasticity deficits in early AD models by Month 22.

The project is highly ambitious and innovative in three distinct ways. First, the combination of real-time genetically encoded biosensor imaging with post-hoc metabolomics on the same animals has not previously been applied to the AD glial metabolism field, providing complementary temporal and biochemical resolution that neither approach can achieve alone. Second, targeting the ANLS as a therapeutic entry point represents a paradigm shift away from amyloid-centric strategies, offering a clinically tractable angle for early intervention. Third, by focusing on the pre-symptomatic phase of AD progression, NEUROGLIA-PF addresses a critical and poorly characterised window for potential therapeutic rescue, contributing original knowledge directly relevant to translational efforts and the emerging field of metabolic neurology.

1.2 Soundness of the Proposed Methodology

The methodology of NEUROGLIA-PF is built around an integrated, three-layer experimental pipeline that combines in vivo optical physiology, ex vivo metabolomics, and targeted functional validation, aligned directly with the four research objectives.

For RO1 and RO2, cranial window implantations will be performed in adult wild-type C57BL/6J mice and age-matched 5xFAD and APP/PS1 AD model mice. Longitudinal two-photon imaging sessions (at 1, 3, 6, and 9 months of age) will deploy co-expressed FRET-based lactate (Laconic) and ATP (Perceval-HR) biosensors delivered via stereotactic AAV injection into cortical layer II/III and hippocampal CA1, with cell-type specificity achieved through GFAP-Cre and CaMKII-Cre driver lines. Ratiometric fluorescence signals will be acquired at sub-micron resolution using a Zeiss LSM 880 NLO multiphoton system, and signal analysis will follow established FRET correction pipelines. To address the known limitation of two-photon imaging depth in scattering tissue (typically

500–800 µm), NEUROGLIA-PF incorporates three complementary mitigation strategies: adaptive optics correction, use of longer excitation wavelengths (1040 nm), and three-photon excitation for deeper hippocampal access. This constitutes a methodological advance in its own right. For RO3, hippocampal and cortical punches from the same animals will be processed for LC-MS/MS-based targeted metabolomics (TCA cycle intermediates, lactate, pyruvate, NAD+/NADH, glutamate, GABA) and untargeted metabolic profiling using a validated HILIC-Orbitrap workflow. Statistical analysis will employ multivariate methods (PCA, OPLS-DA) and network-level pathway enrichment. For RO4, MCT4 gain-of-function will be achieved via AAV-mediated overexpression in astrocytes of AD model mice; synaptic plasticity will be assessed by field recordings of long-term potentiation (LTP) in acute hippocampal slices, and cognition by novel object recognition and Morris water maze.

Interdisciplinary integration is a defining feature of the methodology: the project connects optical biophysics, molecular neuroscience, analytical chemistry, and translational pharmacology. Regarding the sex and gender dimension, all animal experiments will use balanced cohorts of male and female mice, with sex as an explicit biological variable in all statistical models, acknowledging the well-documented sexual dimorphism in AD progression and astrocyte reactivity. Furthermore, the analysis will specifically examine whether the temporal profile of ANLS disruption differs between sexes, contributing novel data to the underexplored question of sex-dependent metabolic vulnerability in neurodegeneration. Open science practices will be rigorously implemented: all imaging datasets and metabolomics raw files will be deposited in publicly accessible repositories (EBRAINS for imaging data; MetaboLights for metabolomics data) under FAIR principles (Findable, Accessible, Interoperable, Reusable) with persistent DOI assignment. A Data Management Plan (DMP) will be submitted by Month 6. All publications arising from NEUROGLIA-PF will be submitted as open access via the institutional agreement with Karolinska Institutet's library and the Horizon Europe open access mandate. Analysis code will be deposited on GitHub under an MIT licence.

1.3 Quality of Supervision, Training and Two-Way Transfer of Knowledge

Prof. Lindqvist is a leading investigator in glial cell biology and metabolic neuroscience at Karolinska Institutet, with a distinguished track record of peer-reviewed publications in journals including Nature Neuroscience, Cell Metabolism, and the Journal of Neuroscience. Prof. Lindqvist has extensive experience in supervising postdoctoral researchers and has successfully mentored fellows through competitive funding schemes including the Swedish Research Council and Horizon Europe. The supervisor's laboratory is uniquely equipped with the two-photon imaging and metabolomics infrastructure central to NEUROGLIA-PF, and maintains active international collaborations with AD research consortia across Europe and North America. Supervision will be structured around weekly one-to-one meetings between the fellow and Prof. Lindqvist, bi-monthly laboratory group meetings, and a six-monthly review meeting with an informal advisory panel comprising two additional senior scientists from Karolinska Institutet. A Personalised Career Development Plan (PCDP) will be established jointly by the fellow and supervisor within the first month and formally reviewed at Month 6, Month 12, and Month 18.

The training programme is designed around both research-specific and transferable competencies. In terms of scientific training, the fellow will acquire mastery of (i) two-photon and three-photon in vivo imaging including cranial window surgery and FRET biosensor analysis, (ii) AAV vector design and stereotactic neurosurgery, (iii) LC-MS/MS metabolomics data acquisition and multivariate analysis, and (iv) acute hippocampal slice electrophysiology. These represent genuine technical advances relative to the fellow's existing expertise in confocal/FLIM microscopy and molecular neurobiology, and will render the fellow one of a small number of researchers worldwide capable of combining all four modalities in a single experimental pipeline. Transferable skills training will be delivered through Karolinska Institutet's structured postdoctoral training programme and will include: scientific writing and manuscript preparation, grant writing (with a dedicated workshop on ERC Starting Grant applications), project management and budgeting, research data management, responsible research and innovation (RRI), science communication for non-specialist audiences, and a course on gender and

diversity in research.

The two-way transfer of knowledge is explicit and substantive. From host to fellow: the fellow will gain access to state-of-the-art multiphoton imaging facilities and the supervisor's deep expertise in astrocyte biology, advanced metabolomics workflows established in the Lindqvist laboratory, and the broad collaborative network of Karolinska Institutet spanning clinical AD research at the associated Memory Clinic. From fellow to host: the fellow brings expertise in molecular neurobiology and FRET sensor development, prior experience with AD mouse model behavioural characterisation across multiple paradigms, proficiency in quantitative fluorescence microscopy analysis pipelines including FLIM-based metabolic readouts, and established connections to the European Alzheimer's research community (EADC, Alzheimer's Research UK ECR Network). These contributions will directly enrich the ongoing research programme of the host group by introducing validated behavioural phenotyping protocols, expanding the group's FRET sensor repertoire, and contributing new analytical capabilities. This mutual enrichment ensures that NEUROGLIA-PF creates lasting value for both the researcher and the host institution beyond the fellowship period.

SECTION 2 - IMPACT

2.1 Career Development and Employability of the Researcher

NEUROGLIA-PF is designed as a transformative step in the career of the fellow, providing a unique combination of technical mastery, scientific leadership experience, and professional network development that will substantially enhance long-term employability within both academic and non-academic sectors. At the outset of the fellowship, the fellow already holds solid expertise in molecular neuroscience and AD models; the training programme will add a highly differentiated technical skill set spanning in vivo optical imaging, metabolomics, and electrophysiology that currently has very few practitioners at the intersection of all these disciplines globally. This positioning makes the fellow highly competitive for independent research positions and translational roles.

The Personalised Career Development Plan (PCDP), established in Month 1 and regularly updated, will serve as the operational framework for career progression. The PCDP will identify short-term milestones (e.g., submission of first NEUROGLIA-PF manuscript by Month 18; preparation of an ERC Starting Grant outline by Month 20), medium-term goals (securing an independent position within two to three years post-fellowship), and long-term aspirations (leading an independent research group focused on glial metabolic neuroscience and/or translational AD therapeutics). The fellowship will provide the fellow with at least two first-author publications in high-impact journals, presentations at two major international conferences (Society for Neuroscience Annual Meeting and Alzheimer's Association International Conference), and active participation in the European MSCA researcher community including attendance at MSCA Alumni events.

In terms of sector-wide employability, the interdisciplinary training and translational angle of the project make the fellow attractive not only to academic institutions but also to the growing number of biotechnology and pharmaceutical companies with metabolic neuroscience programmes (e.g., Denali Therapeutics, Lilly, Roche CNS division). The fellow will benefit from Karolinska Institutet's strong industrial liaison office and innovation ecosystem (KI Innovations, Karolinska Institutet Science Park), through which contact with industry stakeholders in the AD field will be actively sought. By the end of the fellowship, the fellow will have acquired a comprehensive portfolio of independent research experience, leadership in a fully personalised project, advanced technical skills, and a professional network spanning academia and industry, constituting a robust foundation for the next career stage.

2.2 Dissemination, Communication and Exploitation

The dissemination, communication, and exploitation strategy of NEUROGLIA-PF is structured around three target audience tiers: the scientific community, clinical stakeholders, and the general public, with specific activities

mapped to each.

For the scientific community, NEUROGLIA-PF will produce a minimum of two peer-reviewed publications: one focused on the in vivo imaging characterisation of ANLS disruption in AD models (targeting Nature Communications or Cell Reports, submission by Month 18), and one reporting the metabolomics findings and MCT4 rescue data (targeting Brain or the Journal of Neurochemistry, submission by Month 22). Both manuscripts will be submitted as open access in full compliance with the Horizon Europe mandate. Preprints will be posted on bioRxiv prior to journal submission to maximise early community access. The fellow will present findings at a minimum of two international conferences over the project lifetime (SfN Annual Meeting, Month 14; AAIC, Month 20), and all datasets will be deposited in public repositories under FAIR principles as described above. A Communication, Dissemination, and Outreach Plan (CDOP) will be submitted as a formal deliverable by Month 23.

For clinical audiences, the fellow will engage with clinicians and translational researchers through the Karolinska University Hospital Memory Clinic network and participate in at least one clinical-basic science interface symposium. The translational implications of ANLS rescue as a therapeutic target will be communicated via a targeted policy brief distributed through the European Alzheimer's Disease Consortium (EADC) channels. For the general public, the fellow will produce a minimum of three lay-language blog posts or short video summaries on the Karolinska research communication platform and will participate in at least one public outreach event such as the European Researchers' Night. Social media dissemination via institutional channels (LinkedIn, X/Twitter, institutional website) will be used throughout the project to maintain continuous public visibility. Regarding exploitation of results, the team will assess the patentability of the MCT4-based metabolic rescue strategy with support from Karolinska Institutet's innovation office (KI Innovations) and evaluate whether the findings support a spinout or licensing pathway in the medium term. A freedom-to-operate analysis will be initiated at Month 18 to identify any existing IP landscape constraints.

SECTION 3 - IMPLEMENTATION

3.1 Work Plan

WP	Title	Months	PM	Description
WP1	Training, Setup and Project Management	M1-M24	4	This work package covers the foundational activities that underpin the entire project: structured induction training in two-photon imaging and metabolomics workflows, establishment of the cranial wind
WP2	In Vivo Two-Photon Imaging of ANLS Dynamics	M3-M16	10	This work package delivers RO1 and RO2. Longitudinal two-photon imaging of glial and neuronal metabolic biosensors in wild-type and AD model mice across four age time-points, producing a quantitative

WP3	Metabolomics of ANLS Failure	M10-M20	7	This work package delivers RO3. Targeted and untargeted LC-MS/MS metabolomics on hippocampal and cortical tissue from the same animals imaged in WP2, providing the biochemical correlate of the imaging
WP4	Metabolic Rescue Experiments	M12-M22	7	This work package delivers RO4. AAV-mediated MCT4 gain-of-function in astrocytes of AD model mice, followed by electrophysiological assessment of LTP rescue and behavioural cognition testing, establis
WP5	Dissemination, Communication and Outreach	M6-M24	2	This work package covers all scientific dissemination, public communication, and exploitation activities, including conference presentations, open access publication, public outreach events, social me

WP1: Training, Setup and Project Management

This work package covers the foundational activities that underpin the entire project: structured induction training in two-photon imaging and metabolomics workflows, establishment of the cranial window surgical protocol, delivery of mandatory MSCA deliverables (DMP and PCDP by Month 6), ongoing project management and reporting, and final reporting at Month 24. WP1 runs in parallel with all scientific WPs throughout the fellowship and ensures continuous career development and quality management.

T1.1: Induction training in two-photon imaging and AAV surgery - Hands-on training in multiphoton microscopy operation (Zeiss LSM 880 NLO), cranial window surgery, AAV stereotactic injection, and FRET biosensor data analysis pipelines under direct supervision of Prof. Lindqvist and laboratory senior postdoc. Duration: Months 1-4.

T1.2: Transferable skills training - Attendance at Karolinska Institutet postdoctoral training courses: scientific writing, grant writing (ERC Starting Grant workshop), project management, RRI, gender and diversity in research, science communication. Spread across Months 1-22.

T1.3: Project management and reporting - Preparation of Data Management Plan (D1.1, Month 6), Career Development Plan (D1.2, Month 6), six-monthly PCDP reviews with supervisor, and Final Report (D1.3, Month 24). Ongoing administrative coordination with KI grants office.

ID	Deliverable	Due
D1.1	Data Management Plan	M6
D1.2	Personalised Career Development Plan	M6
D1.3	Final Project Report	M24

ID	Milestone	Due	Verification

MS1	Training phase complete and experimental protocols validated	M4	Successful test imaging session with biosensor-expressing mice; supervisor sign-off on protocol log

WP2: In Vivo Two-Photon Imaging of ANLS Dynamics

This work package delivers RO1 and RO2. Longitudinal two-photon imaging of glial and neuronal metabolic biosensors in wild-type and AD model mice across four age time-points, producing a quantitative atlas of ANLS dynamics and its progressive disruption in the preclinical AD phase. This WP constitutes the core experimental engine of the project.

T2.1: Cohort preparation and baseline imaging (wild-type) - Cranial window implantation and AAV injection in wild-type C57BL/6J mice; longitudinal imaging at 1 and 3 months of age; FRET signal acquisition and analysis for Laconic and Perceval-HR. Months 3-9.

T2.2: Longitudinal imaging in AD model mice - Parallel imaging cohorts in 5xFAD and APP/PS1 mice at 1, 3, 6, and 9 months; comparative analysis of lactate and ATP biosensor dynamics relative to plaque deposition (assessed by co-imaged methoxy-X04 amyloid stain). Months 5-16.

T2.3: Data analysis and atlas construction - Automated cell segmentation, FRET ratio extraction, and spatiotemporal mapping using custom Python pipelines; statistical comparison across genotypes, ages, and sexes. Months 10-16.

ID	Deliverable	Due
D2.1	In vivo ANLS imaging dataset deposited in EBRAINS repository	M16
D2.2	Manuscript: In vivo mapping of ANLS disruption in early AD models	M18

ID	Milestone	Due	Verification
MS2	Successful longitudinal imaging at all four time-points in both AD model lines	M12	Complete imaging dataset with minimum n=6 animals per group per time-point; data quality report approved by supervisor

WP3: Metabolomics of ANLS Failure

This work package delivers RO3. Targeted and untargeted LC-MS/MS metabolomics on hippocampal and cortical tissue from the same animals imaged in WP2, providing the biochemical correlate of the imaging phenotypes and identifying the metabolic signature of ANLS failure in AD progression.

T3.1: Tissue collection and LC-MS/MS sample preparation - Microdissection of hippocampal and cortical punches post-imaging endpoint; rapid freeze-clamping; validated HILIC-Orbitrap extraction and analysis for targeted TCA cycle, glycolytic, and neurotransmitter metabolite panels. Months 10-15.

T3.2: Untargeted metabolic profiling and pathway analysis - Untargeted positive and negative mode LC-HRMS acquisition; feature extraction, alignment, and annotation using XCMS and MetaboAnalyst; OPLS-DA and pathway enrichment analysis. Months 14-19.

T3.3: Integrative analysis of imaging and metabolomics data - Correlation of per-animal FRET biosensor trajectories with matched metabolomic profiles; network-level integration using multi-block PLS analysis; preparation of integrated dataset and manuscript. Months 17-20.

ID	Deliverable	Due
D3.1	Metabolomics dataset deposited in MetaboLights	M20
D3.2	Manuscript: Metabolomic signature of ANLS failure in early Alzheimer models	M22

ID	Milestone	Due	Verification
MS3	Targeted metabolomics panel validated and first-pass analysis complete	M15	QC metrics within accepted thresholds; preliminary group separation in PCA visible; report to supervisor

WP4: Metabolic Rescue Experiments

This work package delivers RO4. AAV-mediated MCT4 gain-of-function in astrocytes of AD model mice, followed by electrophysiological assessment of LTP rescue and behavioural cognition testing, establishing proof-of-concept for ANLS-targeted metabolic therapy in early AD.

T4.1: AAV-MCT4 vector preparation and astrocyte-specific delivery - Cloning of GFAP-promoter-driven MCT4 overexpression construct into AAV9 backbone; virus production and titration at KI viral vector core; stereotactic injection into hippocampus of 2-month-old AD model mice. Months 12-15.

T4.2: Electrophysiological assessment of LTP rescue - Acute hippocampal slice preparation at 4 months post-injection; field recordings of Schaffer collateral-CA1 LTP using theta-burst stimulation protocol; comparison of LTP magnitude and decay between MCT4-treated, sham-injected, and wild-type groups. Months 16-20.

T4.3: Cognitive behavioural testing - Novel object recognition, Morris water maze, and open field testing of MCT4-treated versus control AD model mice; sex-stratified statistical analysis. Months 18-22.

ID	Deliverable	Due
D4.1	MCT4 rescue proof-of-concept data report	M22

ID	Milestone	Due	Verification
MS4	AAV-MCT4 astrocyte-specific expression confirmed by immunohistochemistry	M15	Confocal images showing >80% GFAP-positive transduction efficiency in hippocampus; MCT4 protein upregulation confirmed by Western blot

WP5: Dissemination, Communication and Outreach

This work package covers all scientific dissemination, public communication, and exploitation activities, including conference presentations, open access publication, public outreach events, social media engagement, and interaction with clinical and industrial stakeholders.

T5.1: Scientific dissemination and publication - Preparation and submission of two open-access manuscripts; preprint posting on bioRxiv; conference presentations at SfN Annual Meeting (Month 14) and AAIC (Month 20); deposition of datasets in EBRAINS and MetaboLights.

T5.2: Public communication and outreach - Production of three lay-language blog posts for KI research platform; participation in European Researchers' Night; social media updates via KI institutional channels; one policy brief for EADC distribution.

T5.3: Exploitation and IP assessment - Meeting with KI Innovations office (Month 18) to assess patentability of MCT4 rescue strategy; freedom-to-operate analysis; preparation of Communication, Dissemination and Outreach Plan deliverable (D5.1).

ID	Deliverable	Due
D5.1	Communication, Dissemination and Outreach Plan (CDOP)	M23

ID	Milestone	Due	Verification
MS5	First peer-reviewed manuscript submitted	M18	Submission confirmation receipt from target journal

Summary of Deliverables

ID	Title	WP	Due	Type

D1.1	Data Management Plan	WP1	M6	DMP
D1.2	Personalised Career Development Plan	WP1	M6	Report
D1.3	Final Project Report	WP1	M24	Report
D2.1	In vivo ANLS imaging dataset deposited in EBRAINS repository	WP2	M16	Open dataset
D2.2	Manuscript: In vivo mapping of ANLS disruption in early AD models	WP2	M18	Scientific manuscript
D3.1	Metabolomics dataset deposited in MetaboLights	WP3	M20	Open dataset
D3.2	Manuscript: Metabolomic signature of ANLS failure in early Alzheimer models	WP3	M22	Scientific manuscript
D4.1	MCT4 rescue proof-of-concept data report	WP4	M22	Scientific report
D5.1	Communication, Dissemination and Outreach Plan (CDOP)	WP5	M23	Plan/Report

Summary of Milestones

ID	Title	WP	Due	Verification
MS1	Training phase complete and experimental protocols validated	WP1	M4	Successful test imaging session with biosensor-expressing mice; supervisor sign-off on protocol log
MS2	Successful longitudinal imaging at all four time-points in both AD model lines	WP2	M12	Complete imaging dataset with minimum n=6 animals per group per time-point; data quality report approved by supervisor
MS3	Targeted metabolomics panel validated and first-pass analysis complete	WP3	M15	QC metrics within accepted thresholds; preliminary group separation in PCA visible; report to supervisor
MS4	AAV-MCT4 astrocyte-specific expression confirmed by immunohistochemistry	WP4	M15	Confocal images showing >80% GFAP-positive transduction efficiency in hippocampus; MCT4 protein upregulation confirmed by Western blot

MS5	First peer-reviewed manuscript submitted	WP5	M18	Submission confirmation receipt from target journal

Work Plan Timeline

Work Package	M1-M6	M7-M12	M13-M18	M19-M24
WP1	[redacted]	[redacted]	[redacted]	[redacted]
WP2	[redacted]	[redacted]	[redacted]	
WP3		[redacted]	[redacted]	[redacted]
WP4		[redacted]	[redacted]	[redacted]
WP5	[redacted]	[redacted]	[redacted]	[redacted]

WP1 (Training and Management): Months 1-24 (continuous, 4 person-months). WP2 (In Vivo Imaging): Months 3-16 (10 person-months), intensive experimental phase Months 5-12, analysis Months 10-16. WP3 (Metabolomics): Months 10-20 (7 person-months), sample preparation Months 10-15, analysis Months 14-20, integration Months 17-20. WP4 (Metabolic Rescue): Months 12-22 (7 person-months), AAV production Months 12-15, LTP recordings Months 16-20, behaviour Months 18-22. WP5 (Dissemination): Months 6-24 (2 person-months), conference presentations at Months 14 and 20, manuscripts submitted Months 18 and 22, CDOP at Month 23. Total person-months: 30. Note: the sum exceeds 24 months because WPs run in parallel; the effective full-time equivalent effort distributed across concurrent WPs totals 24 person-months of researcher time over the fellowship duration. Key deliverables: D1.1 and D1.2 (Month 6), MS1 (Month 4), MS2 (Month 12), MS3 and MS4 (Month 15), D2.1 (Month 16), D2.2 and MS5 (Month 18), D3.1 (Month 20), D3.2 and D4.1 (Month 22), D5.1 (Month 23), D1.3 Final Report (Month 24). The work plan is structured so that WP2 and WP3 are tightly coupled (shared animal cohorts), WP4 is initiated in parallel with WP3 analysis, and WP5 runs continuously, ensuring no idle periods and a steady output of scientific products throughout the 24-month period.

3.2 Management Structure and Risk Management

The management structure of NEUROGLIA-PF is straightforward, reflecting its nature as a single-fellow action. The fellow holds primary responsibility for the day-to-day execution of the research programme, data management, and preparation of all deliverables and reports. Prof. Lindqvist acts as primary supervisor and scientific mentor, with weekly one-to-one meetings and open-door availability for ad hoc questions. An informal Scientific Advisory Panel (SAP) comprising two additional Karolinska Institutet professors with complementary expertise (one in AD pathology, one in analytical metabolomics) will convene every six months to review progress, provide independent scientific input, and support the fellow's career development. Administrative support will be provided by the Karolinska Institutet grants office, which has extensive experience managing Horizon Europe grants including MSCA actions. Progress will be monitored against the milestones and deliverables schedule defined in Section 3.1, with any delays flagged at the subsequent weekly supervisor meeting and discussed at the next SAP review.

Risk assessment and mitigation: Four principal risks have been identified. Risk 1 – Variability in AD mouse model phenotype (probability: medium; severity: medium). The 5xFAD and APP/PS1 models are known to exhibit variability in plaque deposition rate and behavioural phenotype between colonies and across sexes. Mitigation: use of two complementary AD model lines as pre-planned redundancy; rigorous age-matched cohort design with sex as explicit biological variable; minimum group sizes calculated by a priori power analysis (G*Power, α=0.05, power=0.8); early time-point histological plaque quantification at Month 8 to confirm expected phenotype before committing full cohorts to later experiments. Risk 2 – Two-photon imaging depth limitations in hippocampus (probability: medium; severity: medium). Access to deep hippocampal layers by two-photon excitation is limited by tissue scattering. Mitigation: adaptive optics module available on the KI LSM 880 NLO system; three-photon excitation protocol at 1300 nm as contingency; if hippocampal access remains insufficient, primary analysis will focus on cortical layer II/III where imaging quality is consistently high, and hippocampal data will be supplemented by ex vivo slice imaging. Risk 3 – Delays in AAV production for WP4 (probability: low; severity: high). Custom AAV vector production can encounter quality control failures. Mitigation: AAV cloning and

production will be initiated at Month 12, with a four-week buffer before the first scheduled injection date; the KI viral vector core facility has validated production pipelines for GFAP-promoter constructs; a commercially available GFAP-GFP AAV (positive control) will be run in parallel to confirm injection efficiency independently of the experimental vector. Risk 4 – Metabolomics instrument downtime (probability: low; severity: medium). The LC-Orbitrap platform may experience scheduled or unscheduled maintenance periods. Mitigation: booking priority for MSCA-funded projects at the KI metabolomics core; contingency access to the SciLifeLab national metabolomics facility as a back-up; sample preparation can be completed independently of instrument availability and samples stored at -80°C.

3.3 Institutional Environment and Hosting Arrangements

Karolinska Institutet (KI) is one of the world's leading medical universities, consistently ranked among the top biomedical research institutions in Europe and internationally (QS World University Rankings: top 10 in Medicine). KI is located in Stockholm, Sweden, and maintains a strong commitment to translational research, international collaboration, and researcher career development, fully aligned with the principles of the European Charter for Researchers and the Code of Conduct for the Recruitment of Researchers. The Department of Neuroscience at KI, which will host NEUROGLIA-PF, is a vibrant research environment of over 200 researchers spanning molecular, cellular, systems, and clinical neuroscience, with particular strength in neurodegeneration, glia biology, and brain imaging.

The research infrastructure available to NEUROGLIA-PF is comprehensive and directly matched to the project's needs. The host laboratory has dedicated access to a Zeiss LSM 880 NLO multiphoton system with adaptive optics module, a fully equipped neurosurgery suite for cranial window implantations and stereotactic injections, a high-resolution LC-Orbitrap mass spectrometry platform for metabolomics, and KI's viral vector core facility for AAV production. KI maintains a dedicated animal facility (KM-B) compliant with EU Directive 2010/63/EU on the protection of animals used for scientific purposes, with specialist staff experienced in mouse neuroscience models. High-performance computing resources for image analysis and metabolomics bioinformatics are available through the KI compute cluster and through the National Academic Infrastructure for Supercomputing in Sweden (NAISS).

KI provides comprehensive support services for MSCA fellows, including a dedicated MSCA support office within the Research Support Office, assistance with administrative and financial reporting, access to the KI postdoctoral association for peer networking and career events, and a structured onboarding programme for international researchers that addresses practical matters such as housing, social insurance registration, and language support. KI holds the HR Excellence in Research Award, demonstrating its institutional commitment to providing an open, transparent, and merit-based research environment. The strong clinical linkage with Karolinska University Hospital and the attached Memory Clinic provides unique opportunities for the fellow to connect laboratory findings with clinical AD research, enhancing both the translational relevance of the project and the fellow's professional network.

PART B2

SECTION 4 - CV of the Experienced Researcher

Education

The experienced researcher holds a PhD in Neuroscience, awarded by a recognised European research university. The doctoral thesis investigated molecular mechanisms of synaptic dysfunction in neurodegenerative disease models, combining cell biology, molecular neuroscience, and fluorescence imaging approaches. Prior to the doctorate, the researcher completed a Master of Science degree in Biomedical Sciences and a Bachelor of Science degree in Biology, both with distinction. During doctoral training, the researcher received formal instruction in advanced confocal and fluorescence microscopy, rodent behavioural neuroscience, and molecular cloning techniques.

Research Experience

The experienced researcher has accumulated postdoctoral research experience in the neuroscience of neurodegeneration, with particular focus on synaptic biology, glial cell function, and Alzheimer's disease mouse models. Research contributions to date include characterisation of astrocyte reactivity in amyloid pathology models, development and validation of fluorescent reporter systems for monitoring neuronal metabolic state, and collaborative work on transcriptomic profiling of glial subtypes in AD tissue. The researcher has hands-on expertise in transgenic mouse model management and behavioural phenotyping (Morris water maze, novel object recognition, fear conditioning), immunohistochemistry and confocal imaging, quantitative PCR and Western blotting, and primary cell culture of neurons and astrocytes. Prior experience with fluorescence lifetime imaging microscopy (FLIM) provides a strong technical foundation for the transition to two-photon FRET biosensor imaging planned in NEUROGLIA-PF.

Publications

1. [First Author] et al. (year). Astrocyte reactivity precedes amyloid plaque deposition and correlates with early synaptic loss in 5xFAD mice. Journal of Neuroinflammation. DOI: [to be completed]. 2. [First Author] et al. (year). A genetically encoded FRET sensor reveals dynamic shifts in neuronal NAD+/NADH ratio during network activity. Cell Chemical Biology. DOI: [to be completed]. 3. [Co-author] et al. (year). Single-cell transcriptomics identifies a metabolically distinct astrocyte subpopulation enriched in early Alzheimer's disease hippocampus. Nature Communications. DOI: [to be completed]. 4. [First Author] et al. (year). MCT4 expression is downregulated in reactive astrocytes adjacent to amyloid plaques in human AD brain tissue. Brain Pathology. DOI: [to be completed]. 5. [Co-author] et al. (year). Behavioural and synaptic phenotype characterisation of the APP/PS1 mouse model across sexes at three-, six- and twelve-month timepoints. Disease Models and Mechanisms. DOI: [to be completed].

Other Achievements

The researcher has presented research findings at three international conferences (Society for Neuroscience, FENS Forum, Alzheimer's Association International Conference) and has been invited to give a seminar at two European research institutions. Peer review contributions have been made for journals including Glia, Neurobiology of Aging, and Neuroscience Letters. The researcher has successfully supervised two Master's students and one undergraduate research project student during the doctoral and early postdoctoral periods, demonstrating emerging mentoring capability. The researcher is fluent in English (working language) and has functional proficiency in Swedish, which will facilitate integration into the Karolinska Institutet environment. Membership in the European Dana Alliance for the Brain and the Alzheimer's Research UK Early Career Network provides established links to the broader European neuroscience and dementia research communities.

SECTION 5 - Capacity of the Participating Organisations

Host Organisation Capacity

Karolinska Institutet is a world-leading medical university headquartered in Stockholm, Sweden, with over 6,000 employees and approximately 1,800 doctoral students. KI accounts for the largest share of academic medical research conducted in Sweden and ranks consistently among the top 10 medical universities globally. KI has a strong and successful track record of participation in EU Framework Programmes, including as a beneficiary of numerous MSCA Postdoctoral Fellowships and Doctoral Networks under Horizon 2020 and Horizon Europe. The institution holds the HR Excellence in Research Award, reflecting alignment with the European Charter for Researchers principles. KI's Research Support Office provides dedicated pre- and post-award grant management services, ensuring full administrative compliance with Horizon Europe grant agreement requirements. KI's international research environment, with over 40% of its researchers being international, makes it particularly well suited to hosting MSCA fellows and guarantees an inclusive, multicultural working environment.

Supervisor Profile

Prof. Lindqvist is a Full Professor at the Department of Neuroscience, Karolinska Institutet, with a research programme dedicated to astrocyte metabolic function in neurological disease. Prof. Lindqvist has an extensive publication record in top-tier journals including Nature Neuroscience, Cell Metabolism, and the Journal of Neuroscience. The supervisor holds active grants from the Swedish Research Council (Vetenskapsrådet) and the Swedish Brain Foundation, and has previously led or participated in EU-funded collaborative projects. Prof. Lindqvist has a strong track record of postdoctoral supervision, with former trainees having gone on to secure independent faculty positions, ERC grants, and industry research leadership roles. The supervisor chairs weekly lab meetings and provides structured individual feedback to all group members, ensuring a supportive and scientifically stimulating mentoring environment. Prof. Lindqvist has specific expertise in the ANLS, glial metabolic biosensors, and two-photon in vivo imaging - precisely the technical domains central to NEUROGLIA-PF - making this supervision arrangement exceptionally well matched to the project's ambitions.

Infrastructure and Resources

The host laboratory and Karolinska Institutet more broadly offer a comprehensive suite of infrastructure directly relevant to NEUROGLIA-PF. Key facilities include: a Zeiss LSM 880 NLO multiphoton system with adaptive optics module and non-linear optics capability for two- and three-photon excitation; a dedicated small animal neurosurgery suite with stereotaxic frames, temperature control, and microsurgery tools for cranial window implantation and AAV injection; a KI Viral Vector Core Facility offering cGMP-grade AAV production and quality testing; a high-resolution LC-Orbitrap mass spectrometry platform (Thermo Scientific Orbitrap Exploris 480) for metabolomics within the KI metabolomics core; the KM-B animal facility fully licensed for genetically modified mouse work under EU Directive 2010/63/EU with dedicated transgenic AD model colonies already maintained in-house; access to the KI BioVis imaging and cell analysis core for histology and confocal validation; and high-performance computing infrastructure through NAISS (National Academic Infrastructure for Supercomputing in Sweden) for image analysis and metabolomics bioinformatics. All facilities are staffed by trained core facility personnel who will provide technical support and quality assurance throughout the project.

SECTION 6 - Ethical Aspects

The research activities of NEUROGLIA-PF involve the use of genetically modified mice (5xFAD, APP/PS1, Cre driver lines) and surgical procedures including cranial window implantation and stereotactic AAV injection, classified under EU Directive 2010/63/EU on the protection of animals used for scientific purposes. All animal experiments will be conducted under ethical approval obtained from the Swedish Ethical Review Authority (Etikprövningsmyndigheten) prior to the commencement of any in vivo work. Experimental procedures will adhere strictly to the 3Rs principles (Replacement, Reduction, Refinement); group sizes will be determined by a priori power analysis to minimise animal use while maintaining statistical validity, and all surgical procedures will be performed under appropriate anaesthesia and analgesia with post-operative monitoring protocols in place. Humane endpoints will be clearly defined and applied.

The project involves the use of recombinant adeno-associated virus (AAV9) vectors for in vivo gene delivery. All AAV work will be conducted in a BSL-2 environment in compliance with Directive 2009/41/EC on the contained use of genetically modified micro-organisms, and institutional biosafety approval will be obtained from KI's Biosafety Committee prior to commencing viral vector work. No environmental release of GMOs is involved; all procedures are contained within licensed laboratory and animal facility spaces. The project does not involve human participants, human cells or tissues, personal data collection, or activities in third countries, and therefore GDPR compliance obligations and third-country ethical considerations are not applicable. The research does not involve dual-use concerns, classified information, or materials with potential for deliberate misuse. No clinical trials, patient data, or vulnerable human populations are involved. An ethics self-assessment table will be completed in the Part A administrative submission, declaring the relevant ethical issues (use of animals, use of GMOs) and confirming that all required approvals will be in place prior to grant agreement signature. Any ethics conditions imposed at evaluation will be addressed in full during the grant preparation phase.