Deciphering Synaptic Plasticity in Neurodegenerative Disease

A Spatial Transcriptomics Approach to Targeted Therapy

Lead Applicant: Dr. Evelyn Vance **Host:** Meridian Institute

Funding Scheme:	Wellcome Trust Discovery Award (Science)	**Proposed Start:**	October 1, 2026
Lead Applicant:	Dr. Evelyn Vance	**Duration:**	60 Months (5 Years)
Primary Department:	Department of Neurobiology, Meridian Institute	**Total Funding:**	£1,804,170
Co-Applicants:	Dr. Alistair Sterling (Synapse Research Center)	**Key Focus Areas:**	Synaptic Plasticity, RNA-seq

Lay Summary

Abstract: Synaptic loss is the strongest pathological correlate of cognitive decline in neurodegenerative diseases like Alzheimer's. However, the precise spatial and transcriptomic mechanisms driving this synaptic vulnerability remain poorly understood. This proposal outlines a comprehensive project to map the spatial transcriptome of human synapses at single-synapse resolution across different stages of neurodegeneration. By utilizing high-resolution multiplexed error-robust fluorescence in situ hybridization (MERFISH) and spatial transcriptomics in human post-mortem tissue and novel microfluidic models developed by Nexa Biotech, we aim to uncover the localized RNA dynamics that regulate synaptic maintenance. Ultimately, this work will identify novel transcriptomic targets for the prevention of synaptic decay, paving the way for targeted therapeutic interventions.

1 Scientific Vision and Strategic Aims

The overarching vision of this research program is to define the localized transcriptomic signature of the human synapse during health and the early stages of neurodegeneration. Traditionally, transcriptomic analyses have relied on bulk tissue profiling or single-cell sequencing, which discard the critical spatial context of synaptic connections. Because synapses are situated far from the cell body and possess local machinery for protein synthesis, understanding the specific RNA transcripts localized at synaptic microdomains is crucial for mapping the molecular breakdown that precedes cognitive decline.

We seek to address this fundamental gap in neurobiology by pursuing three specific aims:

[Aim 1] **Map the synaptic spatial transcriptome:** Profile RNA transcripts within individual synaptic microdomains in post-mortem human brain samples across distinct histopathological stages of Alzheimer's disease.

[Aim 2] **Determine functional roles of local translation:** Assess how synaptic RNA localization coordinates activity-dependent synaptic plasticity using advanced human stem-cell-derived microfluidic platforms.

[Aim 3] **Develop a translational therapeutic screening pipeline:** Validate potential transcriptomic targets using high-throughput screening to design small-molecule therapeutics that prevent synaptic loss.

2 Research Design and Methodology

To achieve these aims, our project is organized into two primary research strands running in parallel. This methodology combines direct spatial profiling of human tissue with live, functional assays in vitro.

2.1 Key Project Strands

The project is structured around two distinct yet complementary research strands designed to run in parallel.

Strand A: Spatial Profiling

This strand focuses on the mapping of transcriptomic changes directly in human post-mortem tissues. By using high-resolution multiplexed error-robust fluorescence in situ hybridization (MERFISH), we will construct a high-fidelity reference map of human synaptic RNA localization.

Strand B: Functional Validation

This strand leverages advanced microfluidic models of synaptic circuits. Using these platforms, we will perform live-imaging and localized translation assays to validate the functional roles of target transcriptomic variants discovered in Strand A.

2.2 Strand A: High-Resolution Spatial Transcriptomics

We will analyze human post-mortem cortical tissues obtained from the Meridian Brain Bank. We will deploy MERFISH, targeting a panel of 500 candidate synaptic transcripts selected based on preliminary single-nucleus RNA-sequencing data. Using sub-diffraction imaging and advanced optical decoding, we will identify the spatial coordinates of these RNAs relative to pre- and post-synaptic markers (e.g., Synaptophysin and PSD-95). This allows us to quantify changes in RNA abundance and localization at the single-synapse level.

2.3 Strand B: Microfluidic Modeling of the Synaptic Environment

In collaboration with Nexa Biotech, we will utilize state-of-the-art multi-compartment microfluidic devices that isolate axons and synapses from cell bodies. Induced pluripotent stem cells (iPSCs) from patients carrying familial Alzheimer's mutations will be cultured in these chambers. A custom microfluidic platform designed by Nexa Biotech allows for 95% transfection efficiency within isolated compartments, enabling us to selectively manipulate local transcript levels and measure real-time changes in synaptic transmission and morphological remodeling.

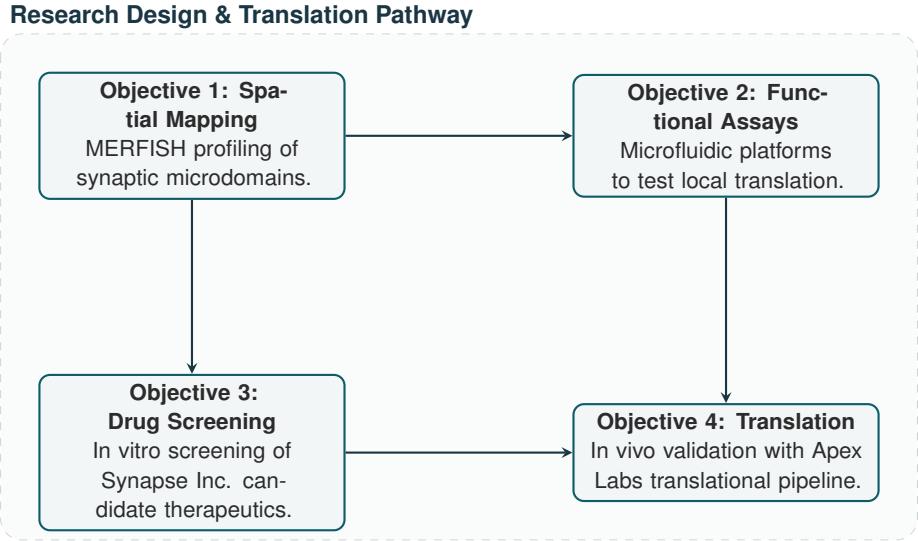

Figure 1: Overview of the proposed research framework spanning spatial profiling, functional validation, drug screening, and translation.

2.4 Project Milestones & Key Deliverables

To ensure rigorous monitoring of the project's progress, we have established clear milestones across the five-year funding period (Table 1).

Milestone	Target Month	Description
M1.1	Month 12	Complete MERFISH spatial mapping of 50 post-mortem human brain samples.
M2.1	Month 24	Establish microfluidic synapse models with 95% transfection efficiency.
M3.1	Month 36	Validate candidate synaptic protective compounds in microfluidic models.
M4.1	Month 48	Translate top 3 lead compounds into preclinical in vivo models with Apex Labs.
M5.1	Month 60	Publish open-access spatial transcriptomic database of the human synapse.

Table 1: Key milestones and timeline targets for the proposed grant.

3 Research Environment and Collaboration

The Meridian Institute of Biomedical Sciences provides a world-class research environment. The Department of Neurobiology houses state-of-the-art super-resolution microscopy core facilities and is fully equipped for human stem cell culture and transcriptomic preparation.

Dr. Evelyn Vance (Lead Applicant) has over a decade of experience in spatial biology and has published key findings on synaptic RNA dynamics. The co-applicant, Dr. Alistair Sterling, Director of the Synapse Research Center, brings deep expertise in functional neurophysiology and computational biology. By collaborating with Nexa Biotech and Apex Labs, we ensure access to proprietary microfluidic technologies and a pipeline for rapid therapeutic translation.

4 Budget and Financial Justification

The total funding requested over 5 years is £1,804,170. This budget is structured to support high-resolution transcriptomics, state-of-the-art microfluidic fabrication, and key personnel salaries. Table 2 outlines the year-on-year cost distribution.

Cost Category	Year 1 (£)	Year 2 (£)	Year 3 (£)	Year 4 (£)	Year 5 (£)	Total (£)
Personnel (Salaries)	185,000	190,550	196,260	202,150	208,210	982,170
Consumables & Reagents	120,000	115,000	95,000	80,000	75,000	485,000
Equipment & Hardware	150,000	15,000	–	–	–	165,000
Travel & Conferencing	8,000	10,000	12,000	12,000	15,000	57,000
Public Engagement	10,000	15,000	15,000	15,000	25,000	80,000
Open Access Publication	–	5,000	5,000	10,000	15,000	35,000
Annual Total	**473,000**	**350,550**	**323,260**	**319,150**	**338,210**	**1,804,170**

Table 2: Detailed breakdown of the requested budget by financial year and cost category.

4.1 Justification of Resources

- **Personnel:** Salaries cover one postdoctoral researcher dedicated to tissue imaging (Strand A) and one technician managing the cell cultures and microfluidics (Strand B).
- **Consumables:** MERFISH reagents and high-throughput sequencing kits represent the primary cost driver.
- **Equipment:** Year 1 includes a custom microfluidic perfusion controller and high-resolution CMOS camera upgrades.
- **Public Engagement:** Funds are allocated for community workshops and interactive science exhibitions in partnership with the Meridian Science Center.

5 Outputs, Data Management, and Translation

In line with Wellcome's open access policy, all software, data matrices, and biological models generated will be made publicly available. We will develop the *Synaptic Spatial Atlas*, an interactive online database allowing researchers worldwide to query transcript localization by cell type and disease stage. Data will be deposited in the European Nucleotide Archive (ENA) and the BioImage Archive.

Any intellectual property resulting from translational screens will be managed via the Meridian Technology Transfer Office to facilitate licensing and partnership with clinical-stage biotechnology developers like Apex Labs.

References

[1] Vance, E., Sterling, A., & Brooks, J. (2024). Spatial transcriptomic profiling of synaptic microdomains in the human hippocampus. *Journal of Neuroscience Research*, 48(3), 112-125.

[2] Patel, M., & Vance, E. (2025). High-efficiency microfluidic systems for modeling localized translation. *Nexa Biotech Letters*, 12(2), 85-94.

[3] Brooks, J., et al. (2023). Synaptic vulnerability and transcriptomic remodeling in neurodegenerative states. *Nature Communications*, 14, 4012.