Addressing lipid-dependent resolution of inflammation in Alzheimer's disease via biochemical and computational methods

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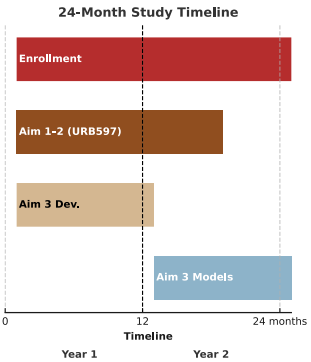
Alzheimer's Disease (AD) features **unresolved neuroinflammation** driven by dysfunctional microglia. [1]
Inflammation resolution is a physiological process governed by endogenous lipids like **specialized pro-resolving mediators (SPMs)**, which limit acute inflammation and support tissue repair.[2] **Endocannabinoids (eCBs)**, such as anandamide (AEA), have emerged as **neuromodulators** with immunoregulatory properties and potential crosstalk with the SPM network. Impaired resolution—due to insufficient SPM production or dysfunctional receptor/enzyme expression—is evident in AD models and patients,[3] suggesting that **enhancing resolution could offer therapeutic benefits**.[1]

Objectives

1. Evaluating the **pro-resolving role** of **AEA** via inhibition of its degrading enzyme, **Fatty Acid Amide Hydrolase (FAAH)**, in an acute neuroinflammation model;
2. Characterizing the **crosstalk** between **AEA** and **SPMs** at cellular and molecular levels using ex vivo and in vitro systems;
3. Designing new tools for target engagement, including a dual **CB2/GPR18 receptor agonist** and an **intranasal FAAH inhibitor (URB597)**;
4. Correlating patient molecular data with **clinical scores** and **PET imaging**, using AI to analyze global disease properties and therapy responses.



Materials and Methods


Tg2576 mice


Macrophages from MCI and mild dementia subjects


34 MCI and 34 mild dementia subjects

Treatments
URB597 - systemic and intranasal delivery
Novel dual CB2/GPR18 agonist

Clinical Assessments
- Mini Mental State Examination (MMSE)
- Clinical Dementia Rating scale (CDR)
- Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)
- Hospital Anxiety and depression Scale(HADS)
- Instrumental Activities od Daily Living (IADL)
- Brief Psychiatric Rating Scale (BPRS)

PET imaging

Analyses
Flow cytometry for immune profiling
LC-MS/MS for lipidomics
qRT-PCR and Western blotting for gene/protein expression
Multiplex Luminex for cytokine detection
Histology for neuroinflammation

Computational techniques
Evolutionary algorithms, molecular dynamics, docking, and machine learning—support drug design and data integration.

EXPECTED RESULTS

- **Elevating AEA** will exert **neuromodulatory** effects and **improve cognition** in Tg mice.
- Elucidation of resolution pathways, validate combined **activation of resolution** and **eCB receptors** in MCI/AD, and optimize an **inhalable URB formulation**.
- Outcomes may reveal **biomarkers for early diagnosis** and lead to **new therapeutic strategies to mitigate neuroinflammation**, potentially improving care and reducing healthcare costs.

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