TARIMAD - TO01000078 - Articles – published in 2023 – Part 1

1. **Time- and Sex-Dependent Effects of Fingolimod Treatment in a Mouse Model of Alzheimer's Disease**

https://doi.org/10.3390/biom13020331

ABSTRACT: Alzheimer's disease (AD) is the most common cause of dementia. Fingolimod has previously shown beneficial effects in different animal models of AD. However, it has shown contradictory effects when it has been applied at early disease stages. Our objective was to evaluate fingolimod in two different treatment paradigms. To address this aim, we treated male and female APP-transgenic mice for 50 days, starting either before plaque deposition at 50 days of age (early) or at 125 days of age (late). To evaluate the effects, we investigated the neuroinflammatory and glial markers, the A_ load, and the concentration of the brain-derived neurotrophic factor (BDNF). We found a reduced A_ load only in male animals in the late treatment paradigm. These animals also showed reduced microglia activation and reduced IL-1_. No other treatment group showed any difference in comparison to the controls. On the other hand, we detected a linear correlation between BDNF and the brain A_concentrations. The fingolimod treatment has shown beneficial effects in AD models, but the outcome depends on the neuroinflammatory state at the start of the treatment. Thus, according to our data, a fingolimod treatment would be effective after the onset of the first AD symptoms, mainly affecting the neuroinflammatory reaction to the ongoing A_ deposition.

2. **TNF Activates the Liver X Receptor Signaling Pathway and Promotes Cholesterol Efflux from Human Brain Pericytes Independently of ABCA1**

https://doi.org/10.3390/ijms24065992

ABSTRACT: Neuroinflammation and brain lipid imbalances are observed in Alzheimer's disease (AD). Tumor necrosis factor-_ (TNF_) and the liver X receptor (LXR) signaling pathways are involved in both processes. However, limited information is currently available regarding their relationships in human brain pericytes (HBP) of the neurovascular unit. In cultivated HBP, TNF_activates the LXR pathway and increases the expression of one of its target genes, the transporter ATP-binding cassette family A member 1 (ABCA1), while ABCG1 is not expressed. Apolipoprotein E (APOE) synthesis and release are diminished. The cholesterol efflux is promoted, but is not inhibited, when ABCA1 or LXR are blocked. Moreover, as for TNF_, direct LXR activation by the agonist (T0901317) increases ABCA1 expression and the associated cholesterol efflux. However, this process is abolished when LXR/ABCA1 are both inhibited. Neither the other ABC transporters nor the SR-BI are involved in this TNF_-mediated lipid efflux regulation. We also report that inflammation increases ABCB1 expression and function. In conclusion, our data suggest that inflammation increases HBP protection against xenobiotics and triggers an LXR/ABCA1 independent cholesterol release. Understanding the molecular mechanisms regulating this efflux at the level of the neurovascular unit remains fundamental to the characterization of links between neuroinflammation, cholesterol and HBP function in neurodegenerative disorders.

3. **Indole Derivatives as New Structural Class of Potent and Antiproliferative Inhibitors of Monocarboxylate Transporter 1 (MCT1; SLC16A1)**

https://doi.org/10.1021/acs.jmedchem.2c01612

ABSTRACT: The solute carrier (SLC) monocarboxylate transporter 1 (MCT1; SLC16A1) represents a promising target for the treatment of cancer; however, the MCT1 modulator landscape is underexplored with only roughly 100 reported compounds. To expand the knowledge about MCT1 modulation, we synthesized a library of 16 indole-based molecules and subjected these to a comprehensive biological assessment platform. All compounds showed functional inhibitory activities against MCT1 at low nanomolar concentrations and great antiproliferative activities against the MCT1-expressing cancer cell lines A-549 and MCF-7, while the compounds were selective

over MCT4 (SLC16A4). Lead compound 24 demonstrated a greater potency than the reference compound, and molecular docking revealed strong binding affinities to MCT1. Compound 24 led to cancer cell cycle arrest as well as apoptosis, and it showed to sensitize these cancer cells toward an antineoplastic agent. Strikingly, compound 24 had also significant inhibitory power against the multidrug transporter ABCB1 and showed to reverse ABCB1-mediated multidrug resistance (MDR).