TARIMAD - TO01000078 - Articles – published in 2022 – Part 2

6. **A Novel Huntington's Disease Assessment Platform to Support Future Drug Discovery and Development**

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ABSTRACT: Huntington's disease (HD) is a lethal neurodegenerative disorder without efficient therapeutic options. The inefficient translation from preclinical and clinical research into clinical use is mainly attributed to the lack of (i) understanding of disease initiation, progression, and involved molecular mechanisms; (ii) knowledge of the possible HD target space and general data awareness; (iii) detailed characterizations of available disease models; (iv) better suitable models; and (v) reliable and sensitive biomarkers. To generate robust HD-like symptoms in a mouse model, the neomycin resistence cassette was excised from zQ175 mice, generating a new line: zQ175Dneo. We entirely describe the dynamics of behavioral, neuropathological, and immunohistological changes from 15–57 weeks of age. Specifically, zQ175Dneo mice showed early astrogliosis from 15 weeks; growth retardation, body weight loss, and anxiety-like behaviors from 29 weeks; motor deficits and reduced muscular strength from 36 weeks; and finally slight microgliosis at 57 weeks of age. Additionally, we collected the entire bioactivity network of small-molecule HD modulators in a multitarget dataset (HD_MDS). Hereby, we uncovered 358 unique compounds addressing over 80 different pharmacological targets and pathways. Our data will support future drug discovery approaches and may serve as useful assessment platform for drug discovery and development against HD.

7. **Screening of Alzheimer's Disease With Multiwavelength Stokes Polarimetry in a Mouse Model**

10.1109/TMI.2021.3129700

A B S T R A C T The minimum histological criterion for the diagnostics of Alzheimer's disease (AD) in tissue is the presence of senile plaques and neurofibrillary tangles in specific brain locations. The routine procedure of morphological analysis implies time-consuming and laborious steps including sectioning and staining of formalin-fixed paraffin-embedded (FFPE) tissue. We developed a multispectral Stokes polarimetric imaging approach that allows characterization of FFPE brain tissue samples to discern the stages of AD progression without sectioning and staining the tissue. The Stokes polarimetry approach is highly sensitive to structural alterations of brain tissue, particularly to the changes in light scattering and birefringence. We present the results of the label-free non-destructive screening of FFPE mouse brain tissue and show several polarization metrics that demonstrate statistically significant differences for tissues at different stages of AD.

8. **Isotope-labeled amyloid-b does not transmit to the brain in a prion-like manner after peripheral Administration**

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ABSTRACT: Findings of early cerebral amyloid-b deposition in mice after peripheral injection of amyloid-b-containing brain extracts, and in humans following cadaveric human growth hormone treatment raised concerns that amyloid-b aggregates and possibly Alzheimer's disease may be transmissible between individuals. Yet, proof that Ab actually reaches the brain from the peripheral injection site is lacking. Here, we use a proteomic approach combining stable isotope labeling of mammals and targeted mass spectrometry. Specifically, we generate 13C-isotope-labeled brain extracts from mice expressing human amyloid-b and track 13C-lysine-labeled amyloid-b after intraperitoneal administration into young amyloid precursor protein-transgenic mice. We detect injected amyloid-b in the liver and lymphoid tissues for up to 100 days. In contrast, injected 13C-lysine-labeled amyloid-b is not detectable in the brain whereas the mice incorporate 13C-lysine from the donor brain extracts into endogenous amyloid-b. Using a highly sensitive and specific proteomic approach, we demonstrate that amyloid-

b does not reach the brain from the periphery. Our study argues against potential transmissibility of Alzheimer's disease while opening new avenues to uncover mechanisms of pathophysiological protein deposition.

9. **Use of PET Imaging to Assess the Efficacy of Thiethylperazine to Stimulate Cerebral MRP1 Transport Activity in Wild-Type and APP/PS1-21 Mice**

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ABSTRACT: Multidrug resistance-associated protein 1 (MRP1, encoded by the ABCC1 gene) may contribute to the clearance of amyloid-beta (Aβ) peptides from the brain into the blood and stimulation of MRP1 transport activity may be a therapeutic approach to enhance brain Aβ clearance. In this study, we assessed the effect of thiethylperazine, an antiemetic drug which was shown to stimulate MRP1 activity in vitro and to decrease Aβ load in a rapid β-amyloidosis mouse model (APP/PS1-21), on MRP1 transport activity by means of positron emission tomography (PET) imaging with the MRP1 tracer 6-bromo-7-[11C]methylpurine. Groups of wild-type, APP/PS1-21 and Abcc1(−/−) mice underwent PET scans before and after a 5-day oral treatment period with thiethylperazine (15 mg/kg, once daily). The elimination rate constant of radioactivity (kelim) was calculated from time–aktivity curves in the brain and the lungs as a measure of tissue MRP1 activity. Treatment with thiethylperazine had no significant effect on MRP1 activity in the brain and the lungs of wild-type and APP/PS1-21 mice. This may either be related to a lack of an MRP1-stimulating effect of thiethylperazine in vivo or to other factors, such as substrate-dependent MRP1 stimulation, insufficient target tissue exposure to thiethylperazine or limited sensitivity of the PET tracer to measure MRP1 stimulation.

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

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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).