TARIMAD - TO01000078 - Articles – published in 2022

1. **Physicochemistry shapes bioactivity landscape of pan-ABC transporter modulators: Anchor point for innovative Alzheimer's disease therapeutics**

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ABSTRACT: Alzheimer‘s disease (AD) is a devastating neurological disorder characterized by the pathological accumulation of macromolecular Aβ and tau leading to neuronal death. Drugs approved to treat AD may ameliorate disease symptoms, however, no curative treatment exists. Aβ peptides were discovered to be substrates of adenosine triphosphate-(ATP)-binding cassette (ABC) transporters. Activators of these membrane-bound efflux proteins that promote binding and/or translocation of Aβ could revolutionize AD medicine. The knowledge about ABC transporter activators is very scarce, however, the few molecules that were reported contain substructural features of multitarget (pan-)ABC transporter inhibitors. A cutting-edge strategy to obtain new drug candidates is to explore and potentially exploit the recently proposed multitarget binding site of pan-ABC transporter inhibitors as anchor point for the development of innovative activators to promote Aβ clearance from the brain. Molecular associations between functional bioactivities and physicochemical properties of small-molecules are key to understand these processes. This study provides an analysis of a recently reported unique multitarget dataset for the correlation between multitarget bioactivity and physicochemistry. Six novel pan-ABC transporter inhibitors were validated containing substructural features of ABC transporter activators, which underpins the relevance of the multitarget binding site for the targeted development of novel AD diagnostics and therapeutics.

2. **Strategies to gain novel Alzheimer’s disease diagnostics and therapeutics using modulators of ABCA transporters**

https://doi.org/10.17879/freeneuropathology-2021-3528

A B S T R A C T Adenosine-triphosphate-(ATP)-binding cassette (ABC) transport proteins are ubiquitously present membrane-bound efflux pumps that distribute endo- and xenobiotics across intra- and intercellular barriers. Discovered over 40 years ago, ABC transporters have been identified as key players in various human diseases, such as multidrug-resistant cancer and atherosclerosis, but also neurodegenerative diseases, such as Alzheimer’s disease (AD). Most prominent and well-studied are ABCB1, ABCC1, and ABCG2, not only due to their contribution to the multidrug resistance (MDR) phenotype in cancer, but also due to their contribution to AD. However, our understanding of other ABC transporters is limited, and most of the 49 human ABC transporters have been largely neglected as potential targets for novel small-molecule drugs. This is especially true for the ABCA subfamily, which contains several members known to play a role in AD initiation and progression. This review provides up-to-date information on the proposed functional background and pathological role of ABCA transporters in AD. We also provide an overview of small-molecules shown to interact with ABCA transporters as well as potential in silico, in vitro, and in vivo methodologies to gain novel templates for the development of innovative ABC transporter-targeting diagnostics and therapeutics.

3. **Binding mode analysis of ABCA7 for the prediction of novel Alzheimer’s disease therapeutics**

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ABSTRACT: The adenosine-triphosphate-(ATP)-binding cassette (ABC) transporter ABCA7 is a genetic risk factor for Alzheimer’s disease (AD). Defective ABCA7 promotes AD development and/or progression. Unfortunately, ABCA7 belongs to the group of ‘under-studied’ ABC transporters that cannot be addressed by small-molecules. However, such small-molecules would allow for the exploration of ABCA7 as pharmacological target for the development of new AD diagnostics and therapeutics. Pan-ABC transporter modulators inherit the potential to

explore under-studied ABC transporters as novel pharmacological targets by potentially binding to the proposed 'multitarget binding site'. Using the recently reported cryogenic-electron microscopy (cryo-EM) structures of ABCA1 and ABCA4, a homology model of ABCA7 has been generated. A set of novel, diverse, and potent pan-ABC transporter inhibitors has been docked to this ABCA7 homology model for the discovery of the multitarget binding site. Subsequently, application of pharmacophore modelling identified the essential pharmacophore features of these compounds that may support the rational drug design of innovative diagnostics and therapeutics against AD.

4. **Structural feature-driven pattern analysis for multitarget modulator landscapes**

https://doi.org/10.1093/bioinformatics/btab832

ABSTRACT: Motivation: Multitargeting features of small molecules have been of increasing interest in recent years.
Polypharmacological drugs that address several therapeutic targets may provide greater therapeutic benefits for patients. Furthermore, multitarget compounds can be used to address proteins of the same (or similar) protein families for their exploration as potential pharmacological targets. In addition, the knowledge of multitargeting features is of major importance in the drug selection process; particularly in ultra-large virtual screening procedures to gain high-quality compound collections. However, large-scale multitarget modulator landscapes are almost non-existent.
Results: We implemented a specific feature-driven computer-aided pattern analysis (C@PA) to extract molecularstructural features of inhibitors of the model protein family of ATP-binding cassette (ABC) transporters. New molecular-structural features have been identified that successfully expanded the known multitarget modulator landscape of pan-ABC transporter inhibitors. The prediction capability was biologically confirmed by the successful discovery of pan-ABC transporter inhibitors with a distinct inhibitory activity profile.

5. **A curated binary pattern multitarget dataset of focused AT P-binding cassette transporter inhibitors**

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ABSTRACT: Multitarget datasets that correlate bioactivity landscapes of small-molecules toward different related or unrelated pharmacological targets are crucial for novel drug design and discovery. AT P-binding cassette (ABC) transporters are critical membrane-bound transport proteins that impact drug and metabolite distribution in human disease as well as disease diagnosis and therapy. Molecular-structural patterns are of the highest importance for the drug discovery process as demonstrated by the novel drug discovery tool 'computer-aided pattern analysis' ('C@PA'). Here, we report a multitarget dataset of 1,167 ABC transporter inhibitors analyzed for 604 molecular substructures in a statistical Binary pattern distribution scheme. This binary pattern multitarget dataset (ABC_BPMDS) can be utilized for various areas. These areas include the intended design of (i) polypharmacological agents, (ii) highly potent and selective ABC transporter-targeting agents, but also (iii) agents that avoid clearance by the focused ABC transporters [e.g., at the blood-brain barrier (BBB)]. The information provided will not only facilitate novel drug prediction and discovery of ABC transporter-targeting agents, but also drug design in general in terms of pharmacokinetics and pharmacodynamics.