

Phenotypic Screening of Novel Compounds for Behavioral Aggression in Alzheimer's Disease

Behavioral aggression is a common neuropsychiatric symptom that coincides with progressive cognitive decline in adults with Alzheimer's disease (AD). Current recommended pharmacotherapies used to treat the aggression and agitation in Alzheimer's patients include antipsychotics, cholinesterase inhibitors, and some antidepressants. However, such interventions either show minimal efficacy or are not well tolerated in the clinic thereby warranting the need for further discovery efforts for therapies with novel mechanisms of actions.

The SmartCube® platform, developed by PsychoGenics, offers an unbiased way to industrialize phenotypic drug discovery for CNS disorders by screening compound libraries in a manner that is agnostic to mechanism, thus often resulting in novel pharmacology. Using this platform, we show here several novel compounds with unknown mechanisms of action and reference screens that were further validated using a mouse model of AD-induced aggression. Specifically, the identified compounds showing a primarily anti-depressant signature were further validated in a mutant mouse line expressing human amyloid precursor protein (APP), namely the APP/PS1 (APP^{sw}/PS1 (m146L) mice using the resident-intruder paradigm to assess male aggression. Data supporting the behavioral characterization of aggression, compound screening using SmartCube® platform and validation of efficacy in a mouse model of amyloidosis will be discussed.