The SmartCube Platform: Use of Phenotypic Screening in Mice with Machine Learning to Identify Novel Antipsychotic Compounds

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INTRODUCTION

While some disease are amenable to high-throughput *in vitro* testing of drug candidates, psychiatric diseases are not. Because psychiatric diseases generally result from disorders of cell–cell communication or circuitry, intact systems are required to detect improvement in disease-relevant endpoints. These endpoints are typically behavioral in nature, often requiring human observation and interpretation.

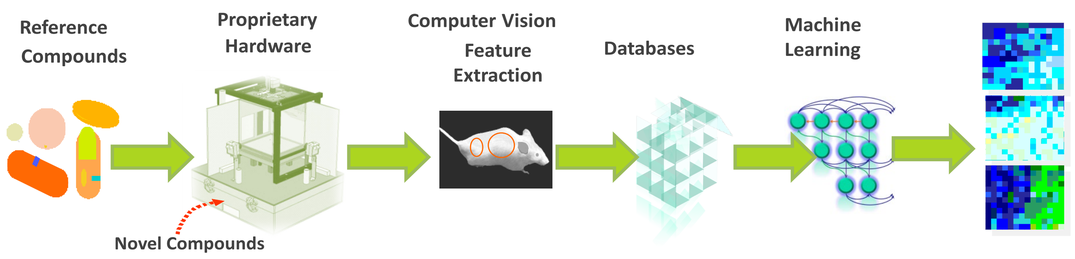
The discovery of neuropharmacologic drugs with novel mechanisms of action is impeded by the absence of high-throughput, robust, and objective behavioral assays. To address this issue, PsychoGenics developed the SmartCube™ platform, an automated system in which behaviors of compound-treated mice are captured by digital video and analyzed with Machine Learning algorithms.

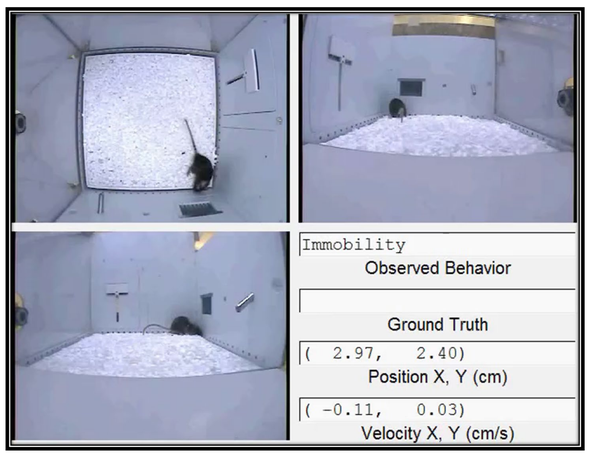
The SmartCube® platform has resulted in the discovery, in partnership with Sunovion, of the novel antipsychotic candidate, SEP-363856 (Ulotaront), which is now in Phase III clinical studies.

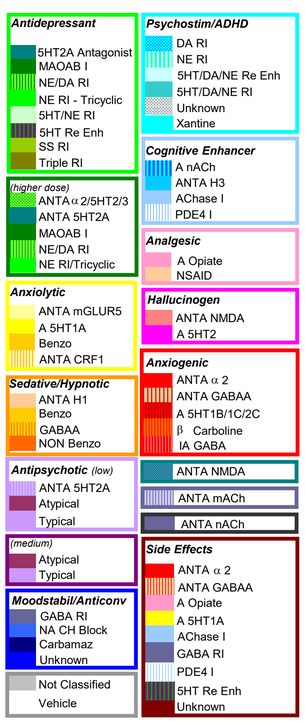
Here we compare and contrast the mouse behavioral signatures obtained from SmartCube for reference antipsychotic compounds and other reference CNS drugs using analytical tools to map the chemical universe of therapeutic drugs and understand the relative position of novel drug candidates.

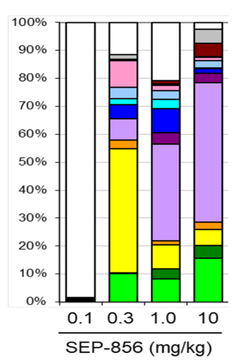
METHODS

Mice are treated with test or reference compounds, administered via IP administration 15 min prior to the study. Mice are then placed in the SmartCube system, which runs through an automated configuration for 45 min involving several behavioral challenges. Behavior of the mice is monitored by high-resolution cameras in each plane, as well as a thermal camera and mechanical actuators. Behavioral features are identified using deep learning, and the overall behavioral activity is analyzed also using machine learning and compared against a library of several hundred behaviorally-active reference drugs and several thousand library compounds. The resulting analyses provides a probability score of similarity to known compounds and defined pharmacologies. Between 8 to 12 mouse are used for each data point.









RESULTS

SmartCube signatures were generated for a range of antipsychotic compounds.

Fig. 1: Typical Antipsychotics

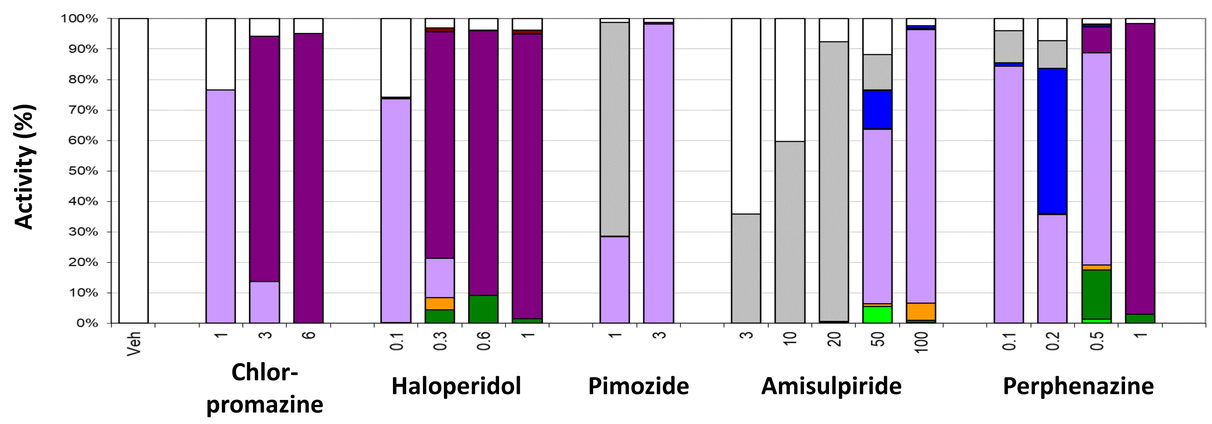


Fig. 2: Atypical Antipsychotics

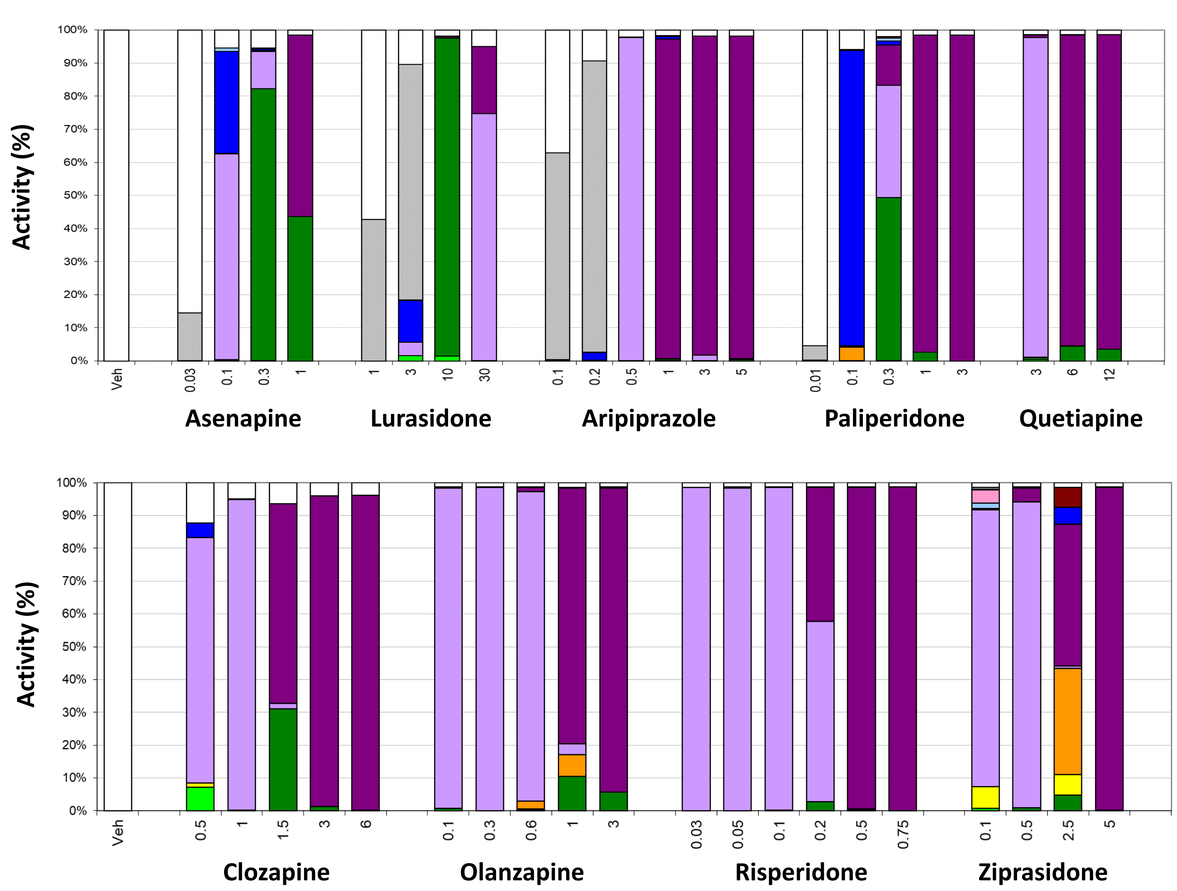
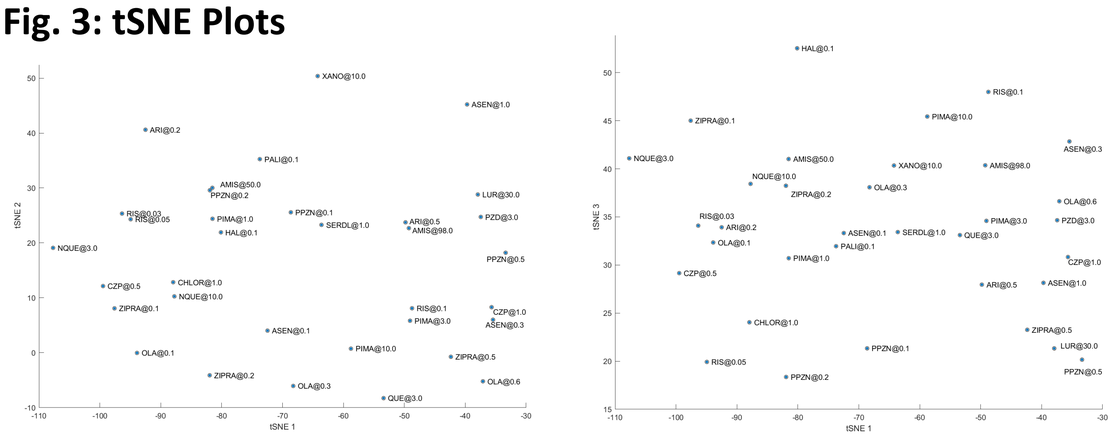


Fig. 3: tSNE Plots



CONCLUSIONS

Reference drugs used for the treatment of schizophrenia produce behaviors in mice after a single dose that are correctly assigned by the SmartCube platform as having antipsychotic (purple) or high-dose antipsychotic (dark purple) activities.

SmartCube was able to detect compounds belonging to the typical and atypical classes of antipsychotics, but in tSNE plots, typical and atypical classes of antipsychotics could not be distinguished from each other following acute dosing. Nonetheless, the SmartCube system is able to detect compounds with antipsychotic activity with different mechanisms of action, as exemplified by the discovery of SEP-856, a compound with TAAR1 and 5-HT1A agonism.