



## In Vitro and In Vivo Validation of Candidate Drugs to Treat Rett Syndrome

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Since the identification of mutations in the methyl-CpG binding protein 2 (MECP2) gene as the cause of Rett syndrome (RTT), much effort has gone into understanding the molecular and cellular mechanisms of the disease. At some point, insights gained at the bench will need to be translated into benefits for RTT patients at the bedside. Mitochondrial deficits (e.g. altered mitochondrial morphology, enzymatic activity, and gene expression) have been observed in RTT patient biopsies, RTT mouse models, neurons differentiated from human embryonic stem cells (hESC) engineered to be deficient in MECP2, and RTT mouse microglia. However, the mitochondrion has not been thoroughly explored as a therapeutic target for treating RTT. We have previously established astrocytes/neurons differentiated from pairs of congenic induced pluripotent stem cells (iPSCs) from RTT patients as cell-based models to study the mechanisms underlying RTT pathogenesis.

Recently, we have identified several mitochondrial deficits in mutant human RTT astrocytes and neurons, as well as primary astrocytes and cortical neurons isolated from Mecp2 knockout mice. While we have learnt some of the cellular and molecular mechanisms underlying the mitochondria phenotypes in both human and mouse astrocytes, the mechanism responsible for these phenotypes in neurons remains unclear. Nonetheless, we recognize that the mitochondrial membrane potential (MMP) phenotype can be easily assessed/quantified in live cells and thus suitable for high throughput screening. Thus, we screened the Selleckchem FDA-approved Drug library for compounds that can rescue the MMP deficit in mutant human RTT astrocytes carrying the R294X mutation. Out of the 1134 compounds in the library, we identified 20 positive hits, among which 13 are known to cross the blood brain barrier (BBB). To test the hypothesis that one or more of those 13 hits could alleviate disease phenotypes in RTT mice, we plan to validate the therapeutic efficacy of those 13 candidate drugs in in vitro and in vivo RTT models. Our proposed study will have significant impact on the development of treatment for RTT, because it is a comprehensive preclinical testing of 13 candidate drugs that correct a fundamental cellular defect in RTT. Since all key cell types (neurons, astrocytes, microglia, and oligodendrocytes) in the brain have been shown to contribute to the disease etiology, targeting a cellular defect that is common to several cell types affected in RTT has the potential to improve the functions of multiple cell types and bring more clinical benefits. Moreover, since those 13 candidate drugs we plan to test have been approved by FDA to treat other diseases (i.e. the safety profile and pharmacokinetics of those drugs are known), if any of them pass our proposed preclinical testing, the chance for it to go to clinical trial and eventually become a drug to treat RTT is high. Finally, success in this project will further establish mutant RTT astrocytes as an in vitro platform for additional drug screens in the future.