PHARMACOLOGICAL SUBTYPES IN SCHIZOPHRENIA: INVESTIGATING THE MOLECULAR DISTINCTIONS USING iPSC NEURONS[1]

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Alterations of neural circuits are thought to contribute to various neuropsychiatric disorders, including schizophrenia. In particular, crosstalk between excitatory (glutamatergic) and dopaminergic neural circuits have been implicated in the pathophysiology of schizophrenia. Intriguingly, two failed antipsychotic trials dictate designation of treatment resistance, advocating the use of clozapine, which is the only antipsychotic indicated for such use. While Dopamine D2 receptor antagonism has been inextricably linked to antipsychotic efficacy, D2 antagonism alone cannot account for efficacy of clozapine in treatment resistant schizophrenia. Emerging evidence from Positron Emission Tomography (PET) of the brain found clear elevations in presynaptic dopamine synthesis only in antipsychotic responsive subgroups. In treatment resistant schizophrenia, presynaptic dopamine synthesis was comparable to healthy controls; instead, elevated glutamate levels in the anterior cingulate cortex was reported on proton magnetic resonance imaging. These evidence suggests two distinct pharmacological subtypes of schizophrenia: (1) antipsychotic responsive for which elevated presynaptic dopamine synthesis has been demonstrated, and (2) treatment resistance, in which glutamatergic neurotransmission has been implicated. Given these findings, we hypothesize that differences at both the neural circuit and synaptic level between responsive versus resistant patients contribute to the resistance of the latter group to standard antipsychotic treatments.

Using induced pluripotent stem cells (iPSCs) reprogrammed from peripheral blood mononuclear cells (PBMCs) collected from identified individuals with antipsychotic responsive and treatment resistant schizophrenia, the project seeks to identify morphological, functional and gene expression differences in dopaminergic and glutamatergic neurons derived from Identification of signature molecular pathways. PBMCs from 12 individuals who are antipsychotic responsive, or treatment resistant or healthy have been identified for reprogramming into iPSCs. 4 of these have been generated and are being characterised. In parallel, we successfully obtained forebrain neurons derived from a pre-existing iPSC line. These mixed population glutamatergic neurons demonstrated morphological maturation and activity as measured using calcium imaging and electrophysiological methods over time, and also expressed a range of pre- and post-synaptic proteins. Collectively, these preliminary data demonstrated that protocols for generation of iPSC and cortical neurons were optimised.

These efforts will not only allow us to elucidate molecular mechanisms contributing to different subclasses of schizophrenia, they will also allow us to design specific treatment strategies to cater for different subgroups of patients.