Markers of potential therapeutic efficacy for negative and cognitive symptoms

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Although antipsychotic drugs alleviate psychotic symptoms of schizophrenia, cognitive deficit and negative symptoms remain an unmet clinical need (Keefe et al. Arch Gen Psychiatry 2007; 64:633-647). In spite of significant efforts by academic groups and the Pharmaceutical Industry, no drug has yet received a license for these indications (see Talpos, Drug Discov Today, 2017; doi: 10.1016/j.drudis.2017.04.014 for recent review). Several key issues remain unresolved, for example, the failure of positive results with new drug candidates in preclinical to Phase II trials to translate into success in large Phase III trials (Bespalov et al. Nat Rev Drug Discov 2016; 15(7):516) and finding a biomarker enabling identification of patients that will transition from an ultra high risk (UHR) state to psychosis. Recent work by Carol Tamminga and colleagues has identified subgroups of patients according to brain based biomarkers not in accordance with their clinical diagnoses (Clementz et al. Am J Psychiatry 2016; 173:373-384). The authors suggest that these subtypes of patients are likely to benefit from differential treatment strategies. The key to development of improved therapies is improved animal models that mimic the human condition in terms of behaviour and pathology and that predict efficacy of novel treatments in patients. The benefit of using animals is development of different models that can represent these separate clinical biotypes. Long-standing research in our laboratory shows that sub-chronic treatment (2 mg/kg ip for 7 days followed by 7 days wash-out) with the un-competitive NMDAR antagonist PCP (Phencyclidine) mimics cognitive and negative symptoms in female Lister Hooded rats, along with associated pathological changes (Neill et al. Pharmacol & Ther 2010;128(3): 419-432; Neill et al. Eur Neuropsych 2014; 24:822-835). These effects are attenuated by atypical antipsychotics, specifically low dose risperidone and novel targets but not by classical antipsychotics. An emerging project in our laboratory shows that maternal immune activation (mIA) induces pathological and behavioural deficits in the offspring that are sex and time dependent and may represent the developmental trajectory of the illness (see Grayson et al. and Oladipo et al, this meeting). Our latest results with novel targets in the scPCP model will be evaluated in this presentation, and recent work with the mIA model. This presentation will consider the evidence that these two animal models may represent separate biotypes, will enhance our understanding of the psycho and neuropathology of specific negative symptom and cognitive domains and allow early detection of novel pharmacological targets.