Precompetitive consortium approach to validation of the next generation of biomarkers in schizophrenia

“\textit{The screening of novel compounds on behavioral task performance and fMRI brain activations in a surrogate patient population (high schizotypes) is a promising approach for the development of the next generation of therapies to treat schizophrenia.}”

Schizophrenia is a debilitating, life-long psychiatric disorder affecting approximately 1% of the world’s population. Available drug therapies comprise typical neuroleptics that act as dopamine $D_2$ receptor antagonists (e.g., haloperidol) and atypical neuroleptics, which have a range of pharmacological actions in addition to $D_2$ receptor blockade (e.g., amisulpride, a $D_2/D_3/5$-HT$_7$, receptor antagonist). Both classes of neuroleptics do not treat all the symptoms of the illness and cause significant side-effects including dyskinesia, obesity and diabetes \cite{1,2}. Patients with schizophrenia exhibit positive and negative symptoms and cognitive deficits \cite{3}. Positive symptoms (visual and auditory hallucinations, delusions and thought disorders) respond to neuroleptics, but the benefit is incomplete. Negative symptoms, such as anhedonia and social withdrawal, can worsen treatment outcomes for patients who do not respond to typical neuroleptics, and atypical neuroleptics have limited efficacy against negative symptoms \cite{4}. Cognitive deficits (disturbances in sensory information processing, attention, working memory and executive functions) are now recognized as a core feature of schizophrenia, but available therapies are generally ineffective \cite{5–7}.

In summary, current therapies are generally effective in treating positive symptoms but have little efficacy in treating negative symptoms and cognitive deficits. Therefore, there is a significant unmet need to develop new drug treatments for schizophrenia that have improved efficacy and fewer side-effects. Despite this need, few new compounds have emerged, and a key determinant of this failure is the high attrition rate in a surrogate patient population in Phase II and III clinical trials \cite{8}. In many cases promising preclinical data have not translated into efficacy in clinical trials in patients \cite{8}. To address this issue of translation, biomarker studies are being conducted early in drug development in healthy volunteers or surrogate patient populations to identify compounds that are likely to fail in late-stage patient trials \cite{9}. An example of a surrogate patient population includes individuals categorized as high schizotypes. Increasing evidence suggests that schizophrenia-spectrum disorders are the extreme end of a trait of psychosis proneness manifested as a personality trait called schizotypy. Schizotypy can be measured using questionnaires such as the Schizotypal Personality Questionnaire (SPQ) and high schizotypes are individuals with personality traits similar to those of patients with schizophrenia \cite{10}. High schizotypes and patients with schizophrenia share many similar features including cognitive deficits, positive symptoms, negative symptoms and anhedonia, although in high schizotypes some or all of these features may present in an attenuated form \cite{11}.

Alternatively, drug challenge can be used as a potential efficacy biomarker, and the $N$-methyl-$\text{d}$-aspartate receptor antagonist ketamine has been proposed as a model for schizophrenia owing to its psychotomimetic properties. Thus, infusion of ketamine in healthy volunteers has been reported to induce both positive and negative symptoms of schizophrenia, and to disrupt cognitive function \cite{12}.

Expertise in efficacy biomarkers and experimental medicine resides largely in clinical academic centers. To be useful in decision-making for novel drug development in schizophrenia, the biomarkers need to be robust and well validated. If a single pharmaceutical company were to attempt to validate biomarker models, progress would understandably be slow and expensive. Hence,
a precompetitive consortium of pharmaceutical companies (members: AstraZeneca, Glaxo-SmithKline, Lundbeck, Organon [a subsidiary of Merck] and Pfizer) was established by the clinical research organisation Pivital and three studies were conducted to validate biomarkers in schizophrenia.

The first study examined the effects of two atypical antipsychotics (amisulpride and risperidone) and a putative cognition enhancer (nicotine) on the performance of a range of behavioral and oculomotor tasks in high schizotypes. This study also determined the feasibility of recruiting high schizotypes in sufficient numbers to support future proprietary compound studies and whether multicenter studies could be successfully executed. In this study, participants were classified into high schizotypes and controls (average schizotypes) measured by the SPQ. In total, 22,373 individuals completed online SPQs and 244 were randomized to take part in the study over a period of 22 months. High schizotypes showed reliable schizophrenia-like abnormalities on four biomarker tasks: salience attribution, antisaccade error rate (an oculomotor control task), n-back and verbal fluency. High schizotypes appeared to have impaired working memory performance relative to controls in tasks that require swift information processing but had normal executive function in paradigms with longer encoding periods [13,14]. The effects of nicotine were enhanced in high schizotypes on the antisaccade and n-back tasks. Amisulpride improved performance in high schizotypes and impaired performance in controls, and this was significant on the n-back and antisaccade tasks.

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The results of previous studies with small samples suggested that SPQ scores (and by inference schizotypy) had a normal distribution in the population, and therefore the control group chosen in the consortium studies comprised individuals with average schizotypy scores. By contrast, the results of this study, which collected over 20,000 scores, suggest that the distribution is highly skewed towards low scores with a median and mode significantly below the mean score [13,14,101]. The control (average schizotypes) group was recruited from scores above the modal score, with the rationale that an extremely low-scoring group might be deviant from the general population norm. This now seems very unlikely given the high proportion of respondents with low scores, and in future studies the most appropriate control group would appear to be low schizotypes. Indeed, the results of a small substudy comparing groups of low, average and high schizotypes on the same set of tasks identified a linear relationship between schizotypy and performance on working memory tasks and error rate on the antisaccade task, suggesting that the most marked differences in performance are between low and high schizotypes [101].

The second study examined behavioral performance and brain activations (BOLD fMRI signals) of high schizotypes and controls (average schizotypes) in two virtual reality mazes designed to assess spatial working memory. The results showed that, although high schizotypes and controls performed equally well on the two tasks, there were significant differences in their brain activations [102]. Thus, reduced activation of the hippocampus and insula was observed during memory encoding in high schizotypes, whereas greater activation of the same regions was observed during memory retrieval. These results appear to indicate that high schizotypes have an inefficient encoding strategy and increased activation of fronto-limbic regions during memory retrieval may be used as a compensatory mechanism to enable comparable task performance to be attained.

Taken together, the results of these studies demonstrate the feasibility of rapidly recruiting high schizotypes in sufficient numbers for experimental medicine studies and provide support for utilizing low and high schizotypy groups and a range of behavioral biomarkers in trials with proprietary compounds.

The third study assessed the performance of healthy volunteers infused with ketamine and pretreated with placebo or risperidone on the same set of biomarkers used in the first schizotypy study to determine whether schizotypy or ketamine infusion best models the deficits in schizophrenia. Unexpectedly, ketamine infusion did not affect performance on most of the biomarker tasks, whereas risperidone generally impaired performance and failed to attenuate the deficits induced by ketamine infusion [103]. An exception was the eye movement task, in which ketamine caused some oculomotor performance deficits similar to those seen in schizophrenia. Thus, ketamine increased saccadic frequency and decreased velocity gain of smooth-pursuit eye movements [15]. However, ketamine did not
influence the antisaccade error rate, latencies or saccadic amplitude gain, which are reported to be impaired in schizophrenia [16], and risperidone had no effects on the ketamine-induced deficits in smooth-pursuit eye movements [15].

The limited effect of ketamine on cognitive biomarkers was surprising and it could be argued that the dose used was too low to show significant effects. However, the target plasma concentration of 100 μg/ml was selected on the basis of previous studies that had demonstrated cognitive deficits at this dose [17].

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 Compared with high schizotypy, ketamine infusion appears to be a less useful model for schizophrenia, at least in terms of the criteria measured in these consortium validation studies.

In conclusion, the successful completion of these studies illustrates the considerable value of a precompetitive consortium approach in developing novel biomarkers for schizophrenia. The validation of experimental medicine models is a time-consuming process, as placebo-controlled trials with both positive and negative controls are required. The model validation process is expensive, challenging and requires meticulous project planning, but the use of marketed drugs, or nonproprietary tool compounds, enables the costs and risks to be shared across a group of pharmaceutical companies to their mutual advantage.

The results of the consortium studies illustrate that the high schizotypy model shows more promise than the ketamine model for efficacy studies, both because the deficits found in high schizotypes are more consistent with those observed in patients with schizophrenia and since there is evidence that some of these deficits are attenuated by antipsychotic and/or cognition enhancer (nicotine) treatment. The screening of novel compounds on behavioral task performance and fMRI brain activations in a surrogate patient population (high schizotypes) is a promising approach for the development of the next generation of therapies to treat schizophrenia. The results of studies with novel, proprietary antipsychotic compounds are awaited with interest to further assess the value of the schizotypy biomarker approach.

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