the potential implications for health and cancer therapy. Given the crucial role of the reward system in emotional processes, our findings offer a new mechanistic insight to the association between the patient’s psychological state, physical health and cancer progression.

### Concurrent Symposia

#### 30. AN IMMUNE PATHOGENESIS OF PSYCHOSIS? EVIDENCE AND CHALLENGES FROM BENCH TO BEDSIDE

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*University of Birmingham*

**Overall Abstract:** The immune pathogenesis story of schizophrenia is gathering momentum, with increasing evidence from animal models, genetic, circulating biomarker and neuropathological studies. Potentially ground breaking new treatment approaches are proposed. However, it is vital that basic science and is equally matched by deep understanding of the complexity of clinical samples and management of multiple confounding factors when moving from bench to bedside. This presentation will pull together key speakers from a variety of fields, demonstrating the need for continued dialogue in translational, and reverse translational, approach. We will present findings from preclinical studies, genetic insights, longitudinal modelling of immune markers from population-based samples and detailed analysis from clinical samples. Data will include evidence of a prenatal immune activation and the potential transgenerational transmission of behavioural and neuronal abnormalities, co-variation of gene sets associated with both increased risk of schizophrenia and immune function (eg CSMD1, DPP4) together with CRP and peripheral inflammatory cytokine association with symptom profiles in both larger population and clinical samples. Thus, evidence presented will move from large data to fine grain analysis, animals to man and from bench to bedside. We aim to provide insights into early pathophysiological processes and forward avenues of research to the ultimate aim of elucidating the immune dysfunction impact on psychosis and future avenues for effectiveness of treatment.

#### 30.2 GENETIC VARIATION RELATED TO IMMUNE FUNCTION AND SCHIZOPHRENIA RISK: EVIDENCE FOR EFFECTS ON COGNITION

Gary Donohoe*  
*1NUI Galway*

**Background:** Altered immune response is associated with many psychiatric disorders, but whether and how these changes confer increased risk remains unclear. In schizophrenia, robust association between illness risk and the MHC region general, and complement component 4 (C4) specifically, has been demonstrated, along with evidence from both gene enrichment and other genetic analysis highlighting the broader role of genetic variation in additional immune related networks to schizophrenia risk.

**Methods:** In a series of recent studies from our group, we examined the effects of immune-related genetic variation, based on gene ontology, implicated in neural function both behaviourally in samples of ~1200 cases and controls, and cortically in samples of ~150 cases and controls.

**Results:** We found that (1) increased predicted C4A RNA expression predicted poorer performance on measures of memory recall (p=0.016, corrected) and a pattern of reduced cortical activity in middle temporal cortex during a measure of visual processing (p<0.05, corrected); (2) variation in a curated gene set associated with both increased Schizophrenia risk and immune function (CSMD1, DPP4, SRPK2, TRIM8, STAT6, FES, EP300, TNFRSF13c) were associated with both variation in both episodic memory and general cognitive ability.

**Discussion:** Based on these findings we conclude that schizophrenia risk associated with variation within immune related genes is likely to be conferred at least partly via effects on cognition, and the molecular mechanisms involved may include effects on inflammatory response.

#### 30.3 ASSOCIATION BETWEEN SERUM C-REACTIVE PROTEIN, POSITIVE AND NEGATIVE SYMPTOMS OF PSYCHOSIS IN A GENERAL POPULATION-BASED BIRTH COHORT

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**Background:** An association between low-grade inflammation and symptoms commonly shared between psychiatric disorders may explain the trans-diagnostic effects of inflammation, and lead to novel mechanistic hypotheses. Schizophrenia includes diverse symptoms, but the relationship...
between low-grade inflammation and specific psychotic symptoms has not been examined.

**Methods:** In the general population-based ALSPAC birth cohort, serum CRP levels were assessed around age 16 years. Ten positive and ten negative symptoms of psychosis were assessed using self-report questionnaires around age 17 years. Associations between CRP and psychotic symptoms were examined using regression analysis before and after controlling for concurrent depressive symptoms, substance use, and other confounders. In addition, we used factor analysis to create positive and negative symptom dimension scores, which were then correlated with CRP.

**Results:** About 13% of 5126 participants reported at least one positive symptom. Paranoid ideation (4.8%), visual (4.3%) and auditory hallucinations (3.5%) were the most common. Negative symptoms were correlated with concurrent depressive (P<0.001), and positive symptoms (P<0.001). CRP was associated with auditory hallucinations and anhedonia after controlling for potential confounders including concurrent depressive symptoms. The adjusted OR for auditory hallucinations for those with high compared with low CRP was 2.67 (95% CI, 1.27–5.60). Evidence for this association remained after excluding participants reporting positive symptoms in the context of cannabis/drug use, physical Illness or sleep, and after excluding participants reporting positive symptoms previously at age 12 years. The adjusted OR for anhedonia per SD increase in CRP was 1.13 (95% CI, 1.01–1.26). Factor analysis revealed similar findings. CRP was associated with both positive and negative symptom dimension scores. There was evidence for interaction between CRP and sex; the associations between CRP and psychotic symptoms were stronger in women.

**Discussion:** Low-grade inflammation may be relevant for auditory hallucinations and anhedonia particularly in women. These findings need replication in other samples especially in patients with psychosis.

### 30.4 Prenatal Infection and Long-Term Brain Pathology: From Preclinical Models to Mechanisms

Juliet Richetto*1

1University of Zurich

**Background:** Prenatal exposure to infection is increasingly recognized to play an important etiological role in neuropsychiatric and neurological disorders with neurodevelopmental components, including schizophrenia, autism, bipolar disorder, and mental retardation. The adverse effects induced by prenatal infection may reflect an early entry into a deviant neurodevelopmental route, but the specificity of subsequent disease or symptoms is likely to be influenced by the genetic and environmental context in which the prenatal infectious process occurs. The epidemiological link between prenatal infection and increased risk of neurodevelopmental disorders also receives strong support from experimental work in animal models. These models are based on maternal gestational exposure to specific infectious agents such as influenza virus or immune activating agents such as the bacterial endotoxin lipopolysaccharide (LPS) or the viral mimic poly(I:C).

**Methods:** Converging evidence form these models suggests that prenatal immune activation can negatively affect early foetal brain development and change the offspring’s neurodevelopmental trajectories, which in turn can lead to the emergence of behavioral and cognitive disturbances in later life. Modelling the human epidemiological association between prenatal infection and increased risk of neurodevelopmental disorders in animals has also greatly advanced our understanding of the underlying mechanisms. According to the prevailing view, cytokine-associated inflammatory events, together with downstream pathophysiological effects such as oxidative stress and (temporary) macronutrient and micronutrient deficiency, seem critical in mediating the post-acute effects of maternal infection on the foetal system.

**Results:** Recent findings have further implicated epigenetic processes as possible molecular mechanisms translating the negative effects of prenatal immune activation on the offspring. Not only does prenatal immune activation cause long-lasting epigenetic modifications such as altered DNA methylation and miRNA expression, but it also causes a transgenerational transmission of behavioral and neuronal abnormalities without additional immune exposures.

**Discussion:** Prenatal infection and associated developmental neuroinflammation may have a pathological role in shaping neurodevelopmental disease risk across generations.

### 31. Optimise-ing the Treatment of First-Episode Schizophrenia

Celso Arango

Hospital General Universitario Gregorio Marañón

**Overall Abstract:** Even if there have been effective antipsychotic treatments for more than fifty years, the implementation of these treatments in clinical practice is still far from optimal, and a significant amount of patients with schizophrenia show poor outcomes. It is unquestionable that antipsychotics remain the first treatment option for patients with first-episode schizophrenia (FES). However, several questions still demand answer in the field. It is unclear how long we should wait before changing an antipsychotic that has not been fully effective, how long we have to wait before starting clozapine in FES, whether we can identify who will respond better to current treatments using biological markers including neuroimaging, and how to improve adherence and functional prognosis after clinical remission is achieved.

OPTImISE (‘Optimisation of Treatment and Management of Schizophrenia in Europe’) is an European Consortium funded under the VII Framework Program that addressed these questions in a sample of nearly 500 patients with FES or schizoaffective disorder and minimal prior exposure to antipsychotics recruited across Europe and Israel. Within an integrative framework, the Consortium aimed at combining clinical, neuroimaging, genetic and biochemical data in a large representative sample to provide answers to these clinically relevant questions and prepare the field for personalised medication strategies as drugs with novel mechanisms of action become available. Results from this study have not yet been published and most of them will be presented for the first time in a Congress.

Based on previous results from the EUFEST study, all patients received amisulpride as a first step. For those not achieving remission after 4 weeks, OPTIMISE compared in a randomised double-blind fashion the option of staying on amisulpride or moving to a drug with a different receptor-binding profile, olanzapine. In those not achieving remission after 6 weeks, clozapine was started. OPTIMISE thus constitutes the first systematic, large-scale testing of the potential benefits of early switching to an antipsychotic with different characteristics in patients not achieving remission, and the application of clozapine in non-remitting patients within the first 10 weeks of treatment. OPTIMISE also provides information on the added value of psychosocial interventions to improve treatment adherence, reduce relapses and improve functional outcomes after remission is achieved, through a 1-year follow-up randomised controlled trial testing a web-based program comprising a motivational intervention package, psychoeducation, and electronic medication alerts and updates.

OPTIMISE also collected blood samples for patients participating in the clinical trial and a systematic sample of more than 200 standardised, high-quality, magnetic resonance imaging (MRI) images. Based on this information, OPTIMISE examined the clinical utility and cost-effectiveness of MRI for screening of underlying organic conditions in FES. In addition, OPTIMISE also offers novel information on how MRI alterations, genetic and biochemical markers at first presentation of schizophrenia can predict the response to subsequent treatment. For this, OPTIMISE used two broad strategies—a combination of technology-driven (pharmacogenetics, proteomics, and metabolomics) and hypothesis-driven (neuroimaging, neurochemical, and immune-related) markers.

This symposium offers an overview of the main results obtained in the project in all these areas, with special focus on their clinical and research implications.