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Applications of blood-based protein biomarker strategies in the study of psychiatric disorders

Man K. Chan [a], Michael G. Gottschalk [a], Frieder Haenisch [a], Jakub Tomasik [a,b], Tillmann Ruland [a,c], Hassan Rahmoune [a], Paul C. Guest [a], Sabine Bahn [a,b,*]

[a] Department of Chemical Engineering and Biotechnology, University of Cambridge, Tennis Court Road, Cambridge CB2 1QT, United Kingdom
[b] Department of Neuroscience, Erasmus MC, Wytemaweg 80, NL-3015 CN Rotterdam, The Netherlands
[c] Department of Psychiatry and Psychotherapy, University Hospital Muenster, Germany

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ABSTRACT

Major psychiatric disorders such as schizophrenia, major depressive and bipolar disorders are severe, chronic and debilitating, and are associated with high disease burden and healthcare costs. Currently, diagnoses of these disorders rely on interview-based assessments of subjective self-reported symptoms. Early diagnosis is difficult, misdiagnosis is a frequent occurrence and there are no objective tests that aid in the prediction of individual responses to treatment. Consequently, validated biomarkers are urgently needed to help address these unmet clinical needs. Historically, psychiatric disorders are viewed as brain disorders and consequently only a few researchers have as yet evaluated systemic changes in psychiatric patients. However, promising research has begun to challenge this concept and there is an increasing awareness that disease-related changes can be traced in the peripheral system which may even be involved in the precipitation of disease onset and course. Converging evidence from molecular profiling analysis of blood serum/plasma have revealed robust molecular changes in psychiatric patients, suggesting that these disorders may be detectable in other systems of the body such as the circulating blood. In this review, we discuss the current clinical needs in psychiatry, highlight the importance of biomarkers in the field, and review a representative selection of biomarker studies to highlight opportunities for the implementation of personalized medicine approaches in the field of psychiatry. It is anticipated that the implementation of validated biomarker tests will not only improve the diagnosis and more effective treatment of psychiatric patients, but also improve prognosis and disease outcome.

Abbreviations: ACE, angiotensin-converting enzyme; ACTH, adrenocorticotrophic hormone; APO, apolipoprotein; ATP4B, H+/K+ ATPase; BDNF, brain-derived neurotrophic factor; CAARMS, comprehensive assessment of at-risk mental states; COX-2, cyclooxygenase-2; CRF, corticotropin-releasing factor; CRFBP, corticotropin releasing factor binding protein; CRH, corticotrophin-releasing hormone; CRP, C-reactive protein; CTGF, connective tissue growth factor; DALYs, disability adjusted life years; DMDA, National Depressive and Manic-Depressive Association; DPP-IV, dipeptidyl-peptidase IV; DPYSL2, dihydropyrimidinase-related protein 2; DSM-IV, diagnostic and statistical manual of mental disorders IV; EGF, epidermal growth factor; ENA-78, epithelial-derived neutrophil-activating protein 78; ESEMeD, European study of the epidemiology of mental disorders; FGF-2, fibroblast growth factor 2; FSH, follicle-stimulating hormone; FT4, free thyroxine 4; GAD1, glutamic acid decarboxylase 1; GFAP, glial fibrillary acid glycoprotein; GLUL, glutamine synthase; GM-CSF, granulocyte macrophage colony-stimulating factor; GPx, glutathione peroxidase; GR, glucocorticoid receptor; GSK3B, glycogen synthase kinase 3 beta; GST, glutathione S-transferase; GWAS, genome-wide association studies; HAM-D, Hamilton depression rating scale; HER-2, human epidermal growth factor receptor 2; HPA, hypothalamic-pituitary-adrenal; ICAM-1, intercellular adhesion molecule 1; ICD-10, International Statistical Classification of Diseases and Related Health Problems 10th Revision; IFN, interferon; IgE, immunoglobulin E; IGF, insulin-like growth factor; IL1b, interleukin 1 beta; IL1-RA, interleukin 1 receptor antagonist; LDL, low density lipoprotein; LPS, lipopolysaccharide; MDA, malondialdehyde; MDC, macrophage-derived chemokine; MHC, major histocompatability complex; MIF, migration inhibitory factor; MIP-1α, inflammatory protein 1 alpha; MIP-1β, macrophage inflammatory protein 1β; MMP, matrix metalloproteinase; NEFL, neurofilament light chain; NFκB, nuclear factor κB; NGF, nerve growth factor; NMDA, N-methyl-D-aspartate; NMR, nuclear magnetic resonance; PANSS, positive and negative syndrome scale; PKA, protein kinase A; ROS, reactive oxygen species; SIPS, structured interview for prodromal syndromes; SOD, superoxide dismutase; SOPS, scale of prodromal symptoms; SSRI, selective serotonin reuptake inhibitor; TGF, tissue growth factor; TIMP-1, tissue inhibitor of metalloproteinases 1; TNFR1, tumour necrosis factor receptor 1; TNF-α, tumour necrosis factor alpha; TPO, thyroid peroxidase; TSH, thyroid-stimulating hormone; TSP-1, thrombospondin-1; UHR, Ultra-High Risk; VEGF, vascular endothelial growth factor; VGLU2, vesicular glutamate transporter 2; WHO, World Health Organization; YLDs, years lived with disability..

* Corresponding author at: Department of Chemical Engineering and Biotechnology, University of Cambridge, Tennis Court Road, Cambridge CB2 1QT, United Kingdom. Tel.: +44 01223334152.
E-mail address: sb209@cam.ac.uk (S. Bahn).

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1. Introduction

More than 450 million people worldwide suffer from a mental disorder, accounting for 13% of the Disability Adjusted Life Years (DALYs) of all diseases and 25% of disability in the Western world. The World Health Organization (WHO) predicts that mental illnesses, especially major depression, will become the most debilitating disorders worldwide by 2030, overtaking cardiovascular disease (World Health Organization, 2010). According to the Global Burden of Disease Study conducted in 2010 (Whiteford et al., 2013), depression, schizophrenia and bipolar disorder account for over 55% of the disease burden attributable to mental and substance use disorders in terms of DALYs. Depressive disorders alone accounted for 40.5% of this burden, schizophrenia for 7.4% and bipolar disorder for 7%. The burden incurred due to years lived with disability (YLDs) was found to be similar to the DALYs figures, with 42.5% for depressive disorders and 7.4% for schizophrenia as well as for bipolar disorder (Whiteford et al., 2013). Although extensive research has led to a better understanding of the biological pathways involved in these disorders, translation into novel therapeutic approaches for diagnosis and treatment has been difficult. Psychiatric disorders are complex disorders which almost certainly share common genetic predispositions, complicating the establishment of boundaries between phenotypes (Cosgrove and Suppes, 2013). As Emil Kraepelin and others had already suspected around a hundred years ago, a definition of disease entities based on clinical observations might not reflect the actual underlying neurobiological phenotype (Regier, 2012).

The current diagnosis of psychiatric disorders is based on the evaluation of symptoms and relies on clinical interview. The diagnosis of a given patient can vary substantially depending on the clinician's experience, training and adherence to the criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5) (American Psychiatric Association, 2000) or the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) (World Health Organization, 1992). To date, no biological tests that are able to objectively evaluate physical or molecular disease correlates are available. Correct diagnosis can also be hampered by the fact that patients with different psychiatric disorders frequently present with similar or identical symptoms (Turck et al., 2009) or indeed deny symptomatology altogether, frequently resulting in misdiagnosis. Misdiagnosis represents a major challenge towards effective disease management and therapeutic intervention. Another problem is that even within a given disease category patient subgroups almost certainly exist. This explains why some patients respond well to certain therapeutic interventions while others persist with severe and even chronic symptom manifestations (Regier, 2012). The existence of subgroups of psychiatric patients is also a major factor in the high attrition rate in psychiatric drug development. Hence, the development of new "blockbuster" drugs has slowed down.