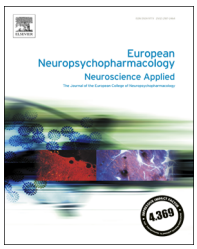
European Neuropsychopharmacology (▮▮▮▮) ▮, ▮▮▮–▮▮▮

www.elsevier.com/locate/euroneuro



Biomarkers for drug development in early psychosis: Current issues and promising directions

Donald C. Goff[a,*], Klaus Romero[b], Jeffrey Paul[c], M. Mercedes Perez-Rodriguez[d], David Crandall[e], Steven G. Potkin[f,*]

[a]*New York University, New York City, NY, USA*
[b]*Critical Path Institute, Tucson, AZ, USA*
[c]*Astellas Pharma Global Development, Northbrook, IL, USA*
[d]*Icahn School of Medicine at Mt. Sinai, New York City, NY, USA*
[e]*Sunovion Pharmaceuticals, Marlborough, MA, USA*
[f]*University of California, Irvine, CA, USA*

Received 15 September 2015; received in revised form 20 January 2016; accepted 23 January 2016

KEYWORDS
Biomarkers;
Psychosis;
Schizophrenia;
Drug therapy;
Genetics;
Inflammation

Abstract
A major goal of current research in schizophrenia is to understand the biology underlying onset and early progression and to develop interventions that modify these processes. Biomarkers can play a critical role in identifying disease state, factors contributing to underlying progression, as well as predicting and monitoring response to treatment. Once biomarker-based therapeutics are established, biomarkers can guide treatment selection. It is increasingly clear that a wide range of potential biomarkers should be examined in schizophrenia, given the large number of genetic and environmental factors that have been identified as risk factors. New models for analysis of biomarkers are needed that represent the central nervous system as a highly complex, dynamic, and interactive system. Many tools are available with which to study relevant brain chemistry, but most are indirect measures and represent only a small fraction of the potential etiologic factors contributing to the molecular, structural and functional components of schizophrenia. This review represents the work of the International Society for CNS Clinical Trials and Methodology (ISCTM) Biomarkers Working Group. It discusses advantages and disadvantages of different categories of biomarkers and provides a summary of evidence that biomarkers representing inflammation, oxidative stress, endocannabinoids, glucocorticoid, and biogenic amines systems are dysregulated and potentially interactive in early phase schizophrenia. As has been recently demonstrated in several neurodevelopmental

*Corresponding authors. Tel.: +1 646 754 4843, +1 94 9 824 8040.
E-mail addresses: Donald.goff@nyumc.org (D.C. Goff), sgpotkin@uci.edu (S.G. Potkin).

http://dx.doi.org/10.1016/j.euroneuro.2016.01.009

Please cite this article as: Goff, D.C., et al., Biomarkers for drug development in early psychosis: Current issues and promising directions. European Neuropsychopharmacology (2016), http://dx.doi.org/10.1016/j.euroneuro.2016.01.009

and neurodegenerative disorders, a multi-modal, longitudinal strategy involving a diverse array of biomarkers and new approaches to statistical modeling are needed to improve early interventions based on the fuller understanding.

1. Definitions and potential roles of biomarkers

As defined by an NIH working group, a biomarker "is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to an intervention"(BDWG, 2001). Biomarkers can be used to make a diagnosis, to stage an illness, to predict diagnostic conversion or estimate prognosis, or to predict and monitor clinical response to treatment (FDA, 2014). Efforts to identify biomarkers that differentiate individuals with schizophrenia from healthy controls or other psychiatric disorders are hampered by the heterogeneity of the phenotype and the diverse assortment of genes and environmental factors that have been associated with the illness. It may be more productive to identify subgroups of individuals who share biological patterns in common that may predict preferential response to targeted treatments rather than attempt to find a "schizophrenia biomarker". In order to guide treatment, biomarkers should reflect disease mechanisms that are relevant to the selection of therapeutic options. Some schizophrenia risk genes and environmental factors are involved early in brain development and may produce alterations in cellular differentiation and connectivity. If measured early enough, biomarkers for these factors might identify individuals at risk in order to modify or halt progression of the aberrant neurodevelopmental process. For example, in mouse models of maternal immune activation, interventions directed at maternal inflammatory cytokines protect against neurodevelopmental abnormalities in their offspring (Ito et al., 2010; Pang et al., 2005). Other risk genes and environmental factors are primarily involved in the biochemistry of signaling pathways; treatments for these individuals may target nodes or hubs in these pathways which can restore a more functional equilibrium. Examples include treatments that reduce inflammation or stress if these factors are found to exacerbate symptoms, or treatments that correct molecular deficits produced by genetic variants, such as folate supplementation in individuals with the MTHFR risk allele (Roffman et al., 2013) or drugs that decrease COMT activity (e.g., tolcapone) in Val158Val COMT polymorphism subjects (Apud et al., 2007). The symptoms of schizophrenia reflect a convergence of diverse etiologic factors upon common pathways or networks which can also be identified by biomarkers and can be targeted pharmacologically, as in the case of dopamine D2 receptor antagonism, which improves psychotic symptoms in most individuals regardless of etiology. However, to substantially improve current outcomes it will be necessary to develop a personalized medicine approach that identifies an individual's relevant genetic and environmental risk factors and the resulting biochemical, functional or structural pathology within a neurodevelopmental context and thereby target individualized therapies.

The FDA in their recent guidance on Drug Development Tools (DDT; Qualification Process for Drug Development Tools; (FDA, 2014)) identifies two separate processes necessary to develop novel biomarkers for drug development. The first step is analytical validation in which the characteristics and performance of assays are quantitatively described, including accuracy, precision, reproducibility, linearity, specificity and sensitivity. The second step defines how the biomarker should be used in the context of clinical management or drug development and includes the biomarker's purpose, its boundaries, the conditions of qualified use, and its interpretation. The largest hurdle is to amass enough clinical data to describe the use and its restrictions (i.e., qualification) in the patient setting. In the clinical research literature, statistically significant differences in mean values of analytes or imaging findings between target populations and controls groups are often interpreted as potential biomarkers. However, the predictive value of a biomarker depends on many factors, including generalizability across clinical populations, the reliability of the biomarker based on elements of sample collection, sample preparation and assay method, the sensitivity and specificity of the biomarker for the specific target population and on the relative prevalence of the target population. Due to issues of poor reliability and generalizability, many promising biomarkers have failed replication and for those biomarkers that have successfully achieved replication, overlap in values between groups may be great enough to make the biomarker of little or no clinical value. Very few publications provide the positive predictive value (PPV), i.e. the ratio of the number of true or accurate positive predictions / total number of positive test predictions (both true and false).

When evaluating peripheral biomarkers, it can be difficult to determine whether they reflect active pathologic factors that may serve as targets for intervention. For example, biomarkers reflecting environmental factors that elevate risk in the perinatal period, such as inflammatory cytokines or folate deficiency, may continue to correlate with disease characteristics in adulthood (Meyer, 2013; Roffman et al., 2011). It is not clear whether these biomarkers identify factors that in adulthood are actively contributing to the illness and can be targeted by therapeutic approaches or are factors that disrupted early brain development and are no longer promising targets for treatment. Even if such biomarkers are no longer drug targets they may be useful in enriching a clinical trial sample by removing unwanted variability. In addition, biomarkers may reflect secondary effects of the illness or treatment rather than etiologic factors. For example, cigarette smoking, metabolic syndrome, insomnia and the stress of psychosis can

Please cite this article as: Goff, D.C., et al., Biomarkers for drug development in early psychosis: Current issues and promising directions. European Neuropsychopharmacology (2016), http://dx.doi.org/10.1016/j.euroneuro.2016.01.009