Biomarkers for Psychiatric Disorders

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Editor

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Springer

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ISSN: xxx-x-xxx-xxxxx-x

e-ISSN: xxx-x-xxx-xxxxx-x

ISBN: 978-1-387-79250-7

e-ISBN: 978-1-387-79251-4

DOI: 10.1007/978-1-387-79251-4

Library of Congress Control Number: 2008930767

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Printed on acid-free paper

springer.com

Preface

Biomarkers are receiving a great deal of attention in the life sciences and the global market for disease - specific biomarkers is expected to see a significant increase in the years to come. Among the different disease areas, psychiatric disorders are without doubt the most challenging in terms of understanding their pathophysiology, drug development and patient treatment. The limited knowledge of etiology and pathogenesis, the great clinical heterogeneity, uncertain phenotype boundaries, genetic overlap between psychiatric disorders and the great influence of non-genetic factors all contribute to this situation.

Although a detailed pathobiology of psychiatric disorders remains elusive, it is now believed that several neural circuits located in more than one area of the brain are involved. There are presumably many ways in which these circuits can be disrupted through the effects of several genes that code for protein products, which in turn have an impact on metabolic and signaling pathways. As a consequence, biomarkers for an apparently similar disease phenotype may vary. Only through an improved understanding of the neural circuitries will it be possible to better stratify different disease phenotypes and identify the relevant biomarkers. Good animal models representing distinct features of a psychiatric disorder phenotype are one way to come up with specific biomarkers. Here a good representation of the relevant psychiatric disease mechanism in an animal disease model is mandatory but challenging, to enable a pre-clinical to clinical study translation.

Not surprising is the fact that because the diagnostic tools used now for psychiatric disorders, which are restricted to the evaluation of behavioral and clinical phenotypes, many scientific studies are compromised. What the field therefore needs more than anything else are specific and sensitive biomarkers instead of the highly variable and subjective clinical parameters currently used to track a disease. This includes biomarkers that are of sufficient sensitivity at the pre-symptomatic stage.

Major challenges for the development of novel psychiatric drugs in the course of clinical trials are the placebo response observed in many patients, side effects and tolerance. Here biomarkers could have a major impact for stratifying placebo responders, an objective which cannot be achieved through knowledge of the genotype alone but which requires markers for acute state assessments. The hope is that biomarkers will benefit drug trials by predicting clinical outcome and reducing development costs through smaller trial size, a concept that will also eventually enable a true personalized-medicine approach. Ultimately biomarkers will be

judged by their clinical utility, in other words whether the added benefit justifies the cost involved. It is now widely believed that only a panel of biomarkers will achieve the necessary specificity and sensitivity for a reliable clinical assay. However, with an increasing complexity of biomarker panels, both measurement and data analysis will become rate-limiting with consequences for regulatory compliance and associated cost. Still, it is my belief that even elaborate diagnostic procedures can be justified if the patient lives longer or feels better.

The road to a successful biomarker consists of several steps that range from discovery, assay development, validation to clinical implementation. The apparent dearth of new biomarkers for psychiatric disorders is on one hand caused by the earlier mentioned patient heterogeneity. At the same time it is apparent that current technologies are still insufficiently sensitive for low abundant marker detection. It therefore may be critical to come up with markers from an array of different platforms including “omics” technologies, *in vivo* imaging, clinical data and others. For this to come about, the science culture has to adapt accordingly. Not only will it be mandatory for specialists of different technology platforms to share and understand each other’s data, but also the various stakeholders including academia, pharma and biotech industries, diagnostic industries, advocacy groups and regulatory agencies need to come up with a concerted effort. Programs have indeed been initiated to bring all the stakeholders to the table: to mention are the *fNIH Biomarkers Consortium* that consists of steering committees, each representing a different disease area including psychiatric disorders. In a related attempt the *Innovative Medicines Initiative* of the *European Union* aims at establishing public-private partnerships between the pharmaceutical industry and academia to support a more efficient discovery and development of better medicines, including the use of biomarkers.

The present book attempts to give an overview of current efforts for psychiatric disorder biomarker discovery. The methods employed for the identification of “wet” biomarkers from brain tissue, body fluids and cells are mainly based on “omics” technologies, including genomics, transcriptomics, proteomics and metabolomics. At the same time neuroimaging and sleep analysis methods are capable of producing “dry” biomarkers. After diagnostic applications, biomarkers used in drug development efforts and the realization of personalized medicine are discussed. Finally, an approach for modeling of psychiatric disorders based on biomarker information and other data sources is submitted, a method that will undoubtedly play an increasingly important role in the understanding of the pathobiology, identification of new drug targets and patient care.

I would like to close by pointing out that the quest for biomarkers for psychiatric disorders is not a novel idea, but was already pursued by the founding director of the *Max Planck Institute of Psychiatry*, Emil Kraepelin (1856-1926). In the late nineteenth century Kraepelin designed a writing scale which was used to measure writing pressure curves of patients suffering from psychiatric disorders. The figure below shows the results of such writing pressure analyses, which Kraepelin used for the classification of mood disorders long before the *Diagnostic and Statistical Manual of Mental Disorders* was published.

Munich, 2008
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Pressure curves recorded by a writing balance. From top to bottom: (I) healthy control, (II) patient with depressed episode, (III) patient with manic episode, (IV) same patient as in (III), after clinical improvement (adapted from E. Kraepelin, *Psychiatry Textbook*, Vol. II, 6th Edition, Leipzig, Verlag von Johann Ambrosius Barth, 1899, p. 373).

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