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Editorial

Editorial: Translational Medicine special issue

This special issue of *Biochemical Pharmacology* brings together a series of articles from leading research scientists and clinicians at the forefront of translational medicine. Different approaches and perspectives on translational methods that are employed at various stages of the drug discovery and development process are reviewed. This information will be of interest to both the general reader and those involved in translational research. In this editorial we briefly outline; (a) what is translational medicine; (b) why biomarkers are needed; (c) the utility of biomarkers; and (d) a synopsis of this special issue of *Biochemical Pharmacology*.

1. What is translational medicine?

Translational medicine, also termed translational research or translational science, has various definitions, all of which describe the transfer of information gained from preclinical drug discovery to the clinic and vice versa [1–3]. The goal of translational science in the pharmaceutical industry is to improve the probability of success in Phase III. Translational medicine focuses on how basic research should be conducted in the context of addressing human pathophysiology [4], while translational research is often more focused on facilitating drug discovery and development. These closely related emerging fields build upon validated clinical methodology to provide minimally invasive, quantitative information that directly affects decision-making at every stage of the discovery and development process, from target identification to proof of concept in clinical trials.

This is achieved largely by the identification, validation and use of biomarkers [5]. These are specific biological substances (*e.g.*, serum cholesterol, blood glucose) or biophysical parameters (*e.g.*, blood pressure, brain volume) that can be monitored objectively and reproducibly to aid in disease diagnosis and to facilitate a rapid and continuous assessment of drug efficacy. Additional benefits of the translational approach include improving the congruency of preclinical animal models to the clinical situation, patient diagnosis and recruitment for clinical trials, and establishing proof-of-concept for efficacy and safety based on a targeted mechanism of action. Such biomarkers are most valuable when "go" or "no-go" decisions must be made, based on a prediction of drug effect or disease outcome. A major challenge with this approach is the time needed to identify and validate a new biomarker for use in the clinical setting.

2. Why do we need biomarkers?

As there are significant unmet medical needs for most neurological and psychiatric disorders, there is a great demand for improved therapeutics. Despite the increasing presence of generic, selective serotonin reuptake inhibitors and atypical antipsychotics, many patients still fail to experience significant symptomatic relief when treated for major depressive and bipolar disorder, or schizophrenia. Therapies that actually modify disease progression have not been identified for any of these conditions, nor for Alzheimer's disease, Parkinson's disease nor other neurodegenerative disorders. Progress in this regard has been frustratingly slow [3]. The pharmaceutical industry has tended to employ a "productivity model" where more money is invested on a larger number of targets on the premise that this will yield a greater number of clinical candidates and new drugs [6–8]. Despite the dramatic increase in expenditures (from approximately $5 billion dollars per year in the 1980's to $45 billion per year in the previous decade), only 21 new drugs were approved in 2010 [9] similar to the annual number approved prior to the use of the productivity model [3]. It is now apparent that a greater emphasis must be placed on translational approaches for drug discovery, including a need for improved congruency from animals to patients.

3. What utility can biomarkers serve?

Definitions of biomarkers differ between, and even within, companies and institutions [5]. One of the most useful classification systems is displayed in Table 1. This utilitarian approach was first devised by Feuerstein et al. [3] and has been adopted and modified at Abbott Laboratories as a way of categorizing and prioritizing translational research [10].

4. Overview of the special issue of *biochemical pharmacology*

The principal aim of this special issue of *Biochemical Pharmacology* is to summarize the current state-of-the-art in translational research with an emphasis on the importance of biomarkers in this approach to drug discovery.

Cognitive endpoints can serve as pharmacodynamic and/or disease biomarkers, providing an effort is made to improve the congruency of preclinical models and clinical endpoints [11]. In an article in this issue entitled "*Translating Cognition from Animals to Humans*", Keeler and Robbins assert that while many animal models have obvious shortcomings in this regard, it is the manner in which these models, and the data derived from them, have been utilized, that accounts for their limitations in making predictions about clinical responses. These authors describe a new focus on cognition models with construct validity, and behavioral assays that test the same cognitive processes across species. As one example, they describe how the stop signal reaction test, which measures an executive function of the prefrontal cortex and related subcortical circuitry, is used to demonstrate a common effect of the

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Table 1
A utilitarian classification of biomarker utility.

Biomarker Purpose	Description
Target Engagement	Typically PET/SPECT tracers. Provides evidence of the physical-chemical interaction of the drug with its target
Pharmacodynamic	Demonstrates the biological consequence/s of a drug action in the exposed organism or patient
Disease Biomarkers or Disease Modification	Biomarkers that correlate best with the disease susceptibility, initiation, progression, remission and relapse. They provide key evidence of whether a drug can alter the disease process
Patient Selection	Biomarkers that indicate the patient most likely to respond (or not respond) to the treatment. Adaptive trial design in clinical trials also represents a type of patient selection biomarker
Target Validation	Biomarkers that provide scientific evidence on the role of the target in the human diseases and its potential as a lead drug discovery and development campaign

norepinephrine transporter inhibitor, atomoxetine, in rodents, healthy volunteers and patients with attention deficit hyperactivity disorder. A key feature of these cognitive endpoints is the common neurocircuitry underpinning a variety of cognitive paradigms that can be tested in rodents, primates, and humans.

This special issue also includes a review by O'Connell et al. entitled "*Schizophrenia Risk Genes: Implications for Future Drug Development*". These authors believe a new approach is needed to identify novel drug targets, modulation of which will result in greater antipsychotic efficacy. They provide examples of how schizophrenia risk genes, such as NRG1, can provide insight into the pathology of this disorder. Such biomarkers can also aid in the selection of patients most likely to respond to a particular treatment or drug class. Biomarker information may also identify those patients who are likely to experience adverse effects to a particular agent or class. They also address the use of genome wide association studies to improve the classification of psychiatric disorders, citing evidence that schizophrenia, bipolar illness and schizoaffective disorder are separate disease entities, although there is some debate on this issue [12,13].

An extensive range of potential pharmacodynamic biomarkers is available. This group includes relatively simple physiological or behavioral measures to integrated physiological and behavioral measures that are dependent on a wide range of neurocircuitry underpinning macrocircuits thought to be involved in mediating disease pathophysiology.

In the article, "*Paradigm Shift in Translational Neuroimaging of CNS Disorders*" Sakoğlu and colleagues highlight the key advantage of neuroimaging. With this technique, the impact of a drug candidate or its interaction with a behavioral/physiological intervention can be determined by examining neural activation and inactivation patterns. Also reviewed in this report are recent developments in structural and functional central nervous system diseases and pain.

Paterson's article "*Translational Research in Addiction: Toward a Framework for the Development of Novel Therapeutics*" reviews the evidence for effective translational approaches for studying substance abuse. Highlighted are obstacles to success that are placed in the context of the search for novel medications for this major unmet medical need.

Physiological EEG measures, such as sleep EEG, can be employed to study and compare results from rodents, healthy human subjects and patients during Phase Ib studies. In their article "*Aligning Strategies for Using EEG as a Surrogate Biomarker: A Review of Preclinical and Clinical Research*" Leiser and colleagues describe how sleep EEG studies are used for this type of translational endpoint, in addition to event-related EEG studies, which have special importance in the discovery and development of antipsychotic drugs.

Flood and colleagues describe in their review "*Developing Predictive CSF Biomarkers: A Challenge Critical to Success in Alzheimer's Disease Translational Medicine*" the use of cerebrospinal fluid biomarkers in neurological and psychiatric disease states, with an emphasis on biomarkers that may be of value in the diagnosis and treatment of Alzheimer's disease. In particular, they discuss how the partnership of the government, pharmaceutical industry, and non-profit organizations serves as a model for advancing the discovery of therapeutics for neurological and psychiatric disease states.

The article by Dawson et al. entitled "*Validation of Experimental Medicine Methods in Psychiatry: The P1vital Approach and Experience*" addresses the potential power of cross industry-academia collaboration by describing the activities of the academic and industry-based consortium, P1VITAL. This approach is based on the capability of executing rapid and reliable decision-making for forwarding experimental therapeutics to Phase II proof of concept studies. Indeed, P1VITAL has reported five novel clinical studies in the areas of anxiety, cognitive disorders, schizophrenia and depression in surrogate patient populations, such as schizotypes instead of schizophrenics and dysphorics instead of those with major depression. These groups are used to test potential biomarkers with reference to gold standard therapies, with imaging and behavioral endpoints assessed and compared.

The translational medicine approaches addressed in this special issue are a critical component an efficient drug discovery program for central nervous system disorders. The use of a range of pharmacodynamic biomarkers, as well as direct measures of central target engagement, allows for greater efficiency in the drug discovery process. The use of central target engagement also defines whether a therapeutic agent tested in Phase II rigorously tests the hypothesis for a given mechanism of action rather than just the clinical effects of the candidate therapeutic.

As detailed in this special issue, the type of data obtained from translational studies is urgently needed to provide feedback to preclinical discovery to move laboratory discoveries to patients as quickly as possible. The need for an effective translational approach for improving productivity in drug discovery is highlighted by recent NIH initiatives establishing the Clinical and Translational Science Awards [14] for training and research in translational science [15].

Given these facts, a special issue of *Biochemical Pharmacology* on translational medicine is both timely and important. It has been a pleasure assembling this group of outstanding scientists in preparing this work and we trust readers will find the end product informative and of practical value in their research.

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