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Current Opinion in Biotechnology

# Metabolomics in pharmaceutical research and development

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Metabolomics has significant potential in pharmaceutical and clinical research, including the identification of new targets, the elucidation of the mechanism of action of new drugs, the characterization of safety and efficacy profiles, as well as the discovery of biomarkers for early disease diagnosis, prognosis, patient stratification, and treatment response monitorization. Metabolomics involves the analysis of small molecules and can lead to an improved understanding of drug candidate actions and to a better selection of targets. Although the application of metabolomics in the pharmaceutical industry is still at its infancy, this experimental approach has the possibility to transform our knowledge of drug action through the examination of drug-induced metabolic pathways associated to both drug efficacy and adverse drug reactions.

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**Current Opinion in Biotechnology** 2015, **35**:73–77

This review comes from a themed issue on **Pharmaceutical biotechnology**

Edited by **Guillermo de la Cueva-Méndez** and **Dror Seliktar**

For a complete overview see the Issue and the Editorial

Available online 17th April 2015

http://dx.doi.org/10.1016/j.copbio.2015.04.004



## Metabolomics

'Omics' approaches are characterized for studying biological systems as a whole, rather than analyzing individual molecules. Each omics science focuses on the study of a particular class of biomolecules: genomics (genes), lipidomics (lipids), transcriptomics (mRNAs), proteomics (proteins) and metabolomics (metabolites), and different analytical platforms are required for carrying out the specific studies.

The metabolome, known as the quantitative description of all endogenous low-molecular weight components (<1 kDa) in a biological sample [1], provides a readout of the metabolic state of an organism under a particular set of conditions. Metabolites are the intermediate and end products of cellular metabolic processes, and their levels (metabolic profile) provide information on the overall phenotype of a system, reflecting the end product of the interaction of the genetic, biochemical, physiological status and environmental exposure [2]. The potential of metabolomics lies in the characterization and quantification of all the metabolites present in a particular biological system, as a function of different variables, using a combination of analytical tools.

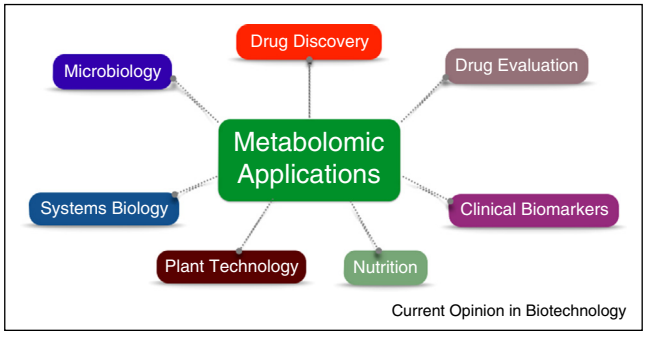
Although the initial metabolomic studies focused on inborn metabolic errors, toxicology, and functional nutrition, nowadays, metabolomics has found application in many other different fields. Thus, during the past two decades, metabolomics approaches have been applied, among others, in: plant biotechnology [3], microbiology [4], food technology [5], and in the preclinical [6–8] and clinical areas [9,10] (Figure 1).

## Metabolomics in pharmaceutical and clinical research

The first step in drug discovery is the identification of chemical hits displaying reasonable affinity for their targets and containing novel chemical scaffolds with the potential to be modified [11]. These initial hits are then evolved to high-affinity ligands through an iterative process involving structure-based drug design and other medicinal chemistry and biochemical approaches. The optimization of the chemical hits is intended to improve affinity, and thus efficacy, but also selectivity. In this context, the more a particular compound has been optimized to bind to the exact sequence and structural characteristics of a specific active site, the less likely it will bind to other proteins. However, success in drug discovery is often hampered by the lack of translational efficacy, an insufficient understanding of the drug mechanism of action, and issues with toxicity associated to off-target effects [12]. These crucial issues pose significant limitations to the current drug discovery process, and explains the need for new developments in this field.

On the other hand, and despite significant advances in drug discovery, not all patients respond favourably to drugs. A significant proportion of patients do not benefit from the therapy, or experience adverse reactions. Thus, it is becoming increasingly recognized that drug treatments should be selected according to the characteristics of each patient in order to improve efficacy and reduce the number and severity of adverse drug reactions [13•,14]. In this context, the identification of new biomarkers able to identify those patients more likely to respond effectively

**Figure 1**

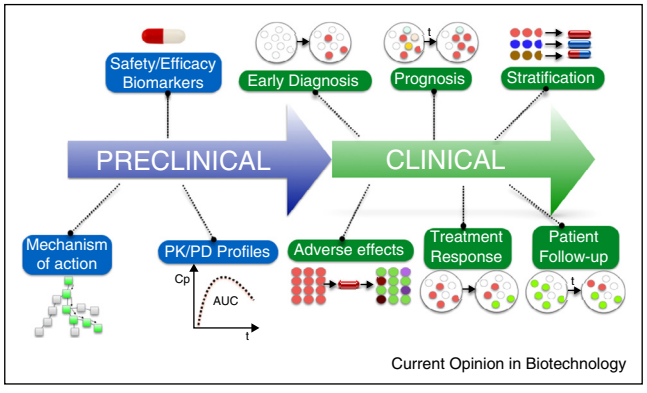



Applications of metabolomics in different research areas.

to a given therapy would translate into an improvement of the existing drug therapies, and into the development of safer and more effective medicines.

A number of systems biology approaches have been proposed to address all these challenges. Among them, metabolomics offers several advantages for tackling the major bottlenecks in drug discovery and development (Figure 2). Thus, metabolomics is characterized for capturing alterations in the metabolism resulting from the interaction among intrinsic properties and extrinsic factor or perturbations. Furthermore, metabolites are easily accessible (e.g., biofluids, cells, tissues, among others), and knowledge about them and the metabolic networks they are involved in have been accumulated for decades. Finally, endogenous metabolites are the same chemical identities, regardless of origin and species, making metabolic biomarkers and their assays valuable and translational throughout the drug discovery and development process [15,16].

**Figure 2**




Potential applications of metabolomics in pharmaceutical research. Small circles correspond to specific patients. Most representative colors (white, red, green) indicate healthy, diseased and responder individuals, respectively.

From a practical point of view, one of the crucial aspects in the metabolomic studies is the selection of an analytical platform. This decision usually depends on the biological matrix to be analyzed and the experimental objectives. Samples that can be analyzed, either directly (i.e., without any further sample preparation) or after a previous extraction [17–19], using this experimental approach range from biofluids (serum [20,21], plasma [22], urine [23], amniotic fluid [24], cerebrospinal fluid [25], among others) to cells or tissues. Recent advances in Nuclear Magnetic Resonance (NMR) spectroscopy [26–28] and mass spectrometry (MS) methods [29,30], the two main technological platforms for carrying out metabolomic studies, have translated into improved sensitivities and spectral resolutions. Both NMR spectroscopy and MS-based methods (e.g., UHPLC–MS, GC–MS, among others) have been successfully applied to numerous *in vitro* and *in vivo* studies [31–36], thus contributing to the significant increase in the number of metabolomic studies published in recent years [37••].

## Target identification

Traditionally, gene and protein expression data have been the preferred source for drug target discovery under the assumption that the most significantly differentially expressed genes or proteins in a disease could provide interesting therapeutic targets [38]. Although this approach has been successful in some cases, in many other examples, overexpressed genes have not been able to provide significant targets either due to their actual function in the cell, regulatory mechanisms inducing overexpression or the ability of a diseased cell to circumvent their inhibition [39].

Interestingly, given the importance of metabolic inhibitors as therapeutic targets (roughly 20% of currently prescribed, FDA-approved drugs target enzymes), the consideration of metabolic networks and metabolomics data in target analysis is leading to a reduction of the number of potentially significant targets [40]. Metabolomics provides the opportunity to pinpoint biochemical changes associated to a particular disease, and then map these variations, that will be important for the development of a pathophysiological condition, in the corresponding metabolic network. Based on this knowledge, crucial proteins can be elucidated and druggable disease targets identified. Metabolomics can also be useful for target validation through the comparison of the metabolic fingerprint of the disease with those obtained when proposed targets are genetically or chemically inhibited [41,42].

## Mechanism of action of drugs

To avoid problems during preclinical or clinical trials, it is desirable that the *in vivo* efficacy and toxicity of any drug candidate is established as soon as possible during the drug discovery process [13•]. In general, unretained