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Metabolomic Signatures for Drug Response Phenotypes-Pharmacometabolomics Enables Precision Medicine

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Abstract

The scaling up of data in clinical pharmacology and the merger of systems biology and pharmacology has led to the emergence of a new discipline of Quantitative and Systems Pharmacology (QSP). This new research direction might significantly advance the discovery, development and clinical use of therapeutic drugs. Research communities from computational biology, systems biology and biological engineering—working collaboratively with pharmacologists, geneticists, biochemists and analytical chemists—are creating and modeling large data on drug effects that is transforming our understanding of how these drugs work at a network level. In this review, we highlight developments in a new and rapidly growing field—pharmacometabolomics—in which large biochemical data-capturing effects of genome, gut microbiome and environment exposures is revealing information about metabotypes and treatment outcomes, and creating metabolic signatures as new potential biomarkers. Pharmacometabolomics informs and compliments pharmacogenomics and together they provide building blocks for QSP.

Keywords

pharmacometabolomics; pharmacometabonomics; metabolomics; metabonomics; pharmacogenomics; biomarkers; clinical pharmacology; systems pharmacology; precision medicine; drug response phenotypes

INTRODUCTION

Diseases involve dysregulation in multiple biochemical pathways. Many disorders are different entities at the molecular level with shared clinical phenotypes. Disease

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heterogeneity, genetic variability, environment and gut microbiome activity contribute to drug response variability. Analytical and computational tools development are transforming our understanding of drug effects, leading to a systems approach in clinical pharmacology. We illustrate such approaches from recent developments in pharmacometabolomics and its union with pharmacogenomics, which provide new approaches for biomarker discovery.

Limitations with Current Therapies and Vision Forward

The past few decades have witnessed a revolution in biomedical research that enabled the move from studying single genes, messenger RNA transcripts, proteins or metabolites to studies encompassing entire genomes, transcriptomes, proteomes and metabolomes. These changes parallel advances in molecular pharmacology, resulting in remarkable therapeutic advances with the development of drugs for treating/controlling human diseases.

However, major challenges remain. Many patients do not respond well to treatments and/or suffer adverse drug reactions, necessitating a more tailored treatment approach. For example, antidepressants, statins, antiplatelet therapies and antihypertensives are widely prescribed medications that have contributed significantly to the management of depression, cardiovascular disease and hypertension, yet their mechanisms of action remain poorly understood with no validated biomarkers to enable effective drug selection for individual patients. Thus, treatment must proceed on a less efficient trial and error basis.

Variability in disease pathophysiology coupled with individual differences in drug response, and the emergence of analytical tools enabling creation of large data reporting on drug effects at a systems level, has resulted in a new field, “Quantitative and Systems Pharmacology” (QSP). The vision for this approach, championed by the National Institute of General Medical Sciences (NIGMS), was developed by leaders in pharmacology, systems biology, pharmacokinetics/pharmacodynamics and computer modeling who articulated their vision in workshops hosted by NIGMS in 2008 and 2010, resulting in the publication of a white paper (http://www.nigms.nih.gov/News/Reports/Pages/201110-syspharma.aspx). Developing and utilizing quantitative systems approaches to pharmacology research could improve the success rates of drug discovery and development, and also lead to deeper mechanistic insights into how drugs work and work differently in different individuals and populations.

In early 2015, President Obama announced a research initiative to accelerate progress toward a new era of Precision Medicine (www.whitehouse.gov/precisionmedicine). Applying this concept broadly will be enabled by the human genome sequence; omics data such as proteomics, metabolomics and genomics; diverse cellular assays; mobile health technology; electronic medical records; and computational tools for analyzing large datasets. Data gathered on large numbers of participants should provide new insights into disease and treatment outcomes.

This bold vision above can transform our understanding of human disease and response to treatment and enable the discovery and development of signatures as biomarkers where a collection of biological measures instead of one marker can inform about outcomes. This information can complement currently used approaches.

Metabolomics, Scaling Up Biochemical Knowledge - New Opportunities for Biomarker Discovery

Knowledge about metabolism plays a key role in medical science and practice. Clinical assays and a small panel of biochemical measures are used in the medical decision process, e.g. screens for inborn errors of metabolism or the measure of LDL/HDL (low-density lipoprotein/high-density lipoprotein) cholesterol for assessing the risk of cardiovascular disease. Biochemical knowledge is also critical for drug discovery and development since drugs often target enzymes, receptors and transporters. Thus, biochemical analysis can help define drug action and off-target effects that can result in adverse reactions. However, measuring only a few metabolites is insufficient to address the complexity of human disease and drug effects.

Scaling knowledge of genes, transcripts and proteins to the “omics” level was recently followed by a similar process of scaling biochemistry to “metabolomics”, the global science of biochemistry (1–2). We can now move beyond the study of one metabolite or pathway to comprehensive study of metabolic networks and the “metabolome”. The metabolome represents the entire repertoire of small molecules present in cells, tissues or body fluids. Their identities, concentrations and fluxes represent the final products of cellular interactions that extend from gene sequence to gene expression, protein expression and, ultimately, the total cellular environment (including drug exposure). The co-metabolism and close interactions between human and gut microbiome is emerging (3), and it seems to contribute significantly to response mechanisms for many therapies (see below). A wide range of metabolomics and lipidomics platforms were recently developed, enabling identification and quantification of a large number of metabolites. This makes it possible to scale up knowledge from one metabolite to thousands, which can better report on disease and drug effects (1,2). Metabolic signatures are starting to emerge as new types of biomarkers for disease and for response to treatment.

Pharmacometabolomics – Novel Tools for Drug Response Phenotyping

The application of metabolomics for studying drug effects was pioneered by the Pharmacometabolomics Research Network (http://pharmacometabolomics.duhs.duke.edu/) and through a partnership with the Pharmacogenomics Research Network (http://pgrn.org/display/pgrnwebsite/PGRN+Home), enabled by President Obama stimulus funding. Drs. Michael Roger’s leadership and vision, along with Drs. Rochelle Long and Richard Okita from NIGMS set up the collaborations between the two and saw how such interactions could help build foundations for the quantitative systems pharmacology approach mentioned above. Seventeen academic centers worked collaboratively to provide novel insights about mechanisms of action and mechanisms of response variation to key drugs used to treat neuropsychiatric disorders and cardiovascular disease (Table 1) (4–22). Pharmacometabolomics studies involve determining an individual’s metabolic state as influenced by environment, genetics and gut microbiome—“metabotype”—to define signatures pre- and post-treatment that might inform treatment outcomes. Pharmacometabolomics also provides tools for mapping drug effects on metabolism and for identifying pathways that contribute to drug response phenotypes (Figure 1A). Baseline information on metabotypes, combined with signatures for drug exposure, can potentially be

used to better define mechanisms of variation in response to drug therapy. Below, we summarize novel concepts that have established foundations for pharmacometabolomics, a new field that complements and informs pharmacogenomics.

A. Metabotypes Inform About Treatment Outcomes and Help Sub-Classify Disease—Using targeted and non-targeted lipidomics and metabolomics platforms, samples from 148 participants enrolled in the Cholesterol and Pharmacogenetics study of simvastatin were profiled (Table 1) (13–16). One hundred were selected from across the LDL cholesterol response distribution; 48 were selected from upper and lower tails of response. Over 500 metabolites were measured in each participant using four complementary metabolomics and lipidomics platforms and were used to predict treatment outcomes or compare good and poor responders. Cholesterol ester and phospholipid classes (lipidomics platform) and several secondary bile acids produced by gut microbiome (sterol bile acids platform) correlated with treatment outcomes (13, 15–16). Using metabolomics data generated by GCTOF platform (gas chromatography time-of-flight mass spectrometry) (14), orthogonal partial least square discriminant analysis was used to compare baseline metabolite levels in good and poor responders, achieving a prediction accuracy of 74% with 70% sensitivity and 79% specificity. The ROC (receiver operating characteristic curve) of true positive rate vs. false positive rate yielded an area under the curve of 0.84. In general, modeling of these metabolites yielded a robust predictive tool for distinguishing good and poor responders. Metabolites that contributed to their separation included xanthine, 2-hydroxyvaleric acid, succinic acid, stearic acid and fructose. This modeling supports the hypothesis that individuals in the tails of the response distribution comprised metabolically distinct subgroups and that their metabolic profiles (metabotypes) might contribute to their differing responses.

Similar studies were conducted with other classes of therapies, confirming the concepts above (Table 1). For example, in studies with sertraline (a selective serotonin reuptake inhibitor [SSRI] used for treating depression), targeted LCECA platform (Liquid Chromatography Electrochemical Array) used for study of neurotransmitters identified signatures at baseline that discriminated between responders and non-responders to drug and to placebo, the first study in humans to illustrate that metabotypes inform about treatment outcomes (4). Although these studies have been relatively small in size and are hypothesis-generating, the data clearly suggests that metabotypes of individuals inform about treatment outcomes and can lead to the development of metabolic signatures as biomarkers of response and the sub-classification of patients for streamlining clinical trials.

Studies with other classes of drugs like beta blocker atenolol used for hypertension (17), the antiplatelet drug aspirin (7, 19,20), the mood stabilizer lithium (11–12) and three anti psychotics (8, 21–22) also revealed major impact of the drugs on metabolism and hence on the metabolic network. Ethnic and gender differences were noted in these metabolic signatures.

B. Metabolic Signatures of Drug Exposure - Signatures of Response— Studies (Table 1, Figure I) (4–22) revealed that most drugs induced many metabolic changes, reflecting effects on multiple interconnected metabolic pathways and networks.

Such metabolic signatures brought new insights about mechanism of action of drugs and placebo and highlighted pathways implicated in response.

For example, lipidomics studies with simvastatin in good and poor responders (Figure 1B) (16) revealed major differences in drug impact on lipid metabolism. In poor responders, the major drug effect was on the cholesterol ester (CE) lipid class; while in good responders, a large number of lipid classes were impacted including phosphatidylcholines (PC), phosphatidylethanolamine (PE) and triglycerides (TG). Response correlated with changes in CE and PC. Metabolomics studies with simvastatin also revealed totally new insights with major additional pathways were affected and some implicated in response (Figure 1C) (14).

Studies with sertraline using targeted metabolic profiling for neurotransmitters illustrated major changes within tryptophan, tyrosine and related purine pathways, with good responders enabling tryptophan metabolism to shift from producing kynurenine to producing melatonin and methoxyindoles (Table I) (1, 4, 5). Using non-targeted metabolomics platforms, major metabolic changes were noted in tricarboxylic acid (TCA) and urea cycles, fatty acids and intermediates of lipid biosynthesis, amino acids, sugars and gut-derived metabolites (Table I) (6) (1). Metabolic changes were far more extensive after 4 weeks of treatment. Pathway analysis in the sertraline group suggested a drug effect on ATP-binding cassette and solute transporters, fatty acid receptors and transporters, G signaling molecules and regulation of lipid metabolism. Correlation between biochemical changes and treatment outcomes suggested a strong association with changes in levels of branched chain amino acids (BCAAs). In the placebo group, lower levels of lactic acid, higher levels of TCA/urea cycle intermediates, and 3-hydroxybutanoic acid correlated with better treatment outcomes. Study results indicated that biochemical changes induced by the drug continue to evolve over 4 weeks of treatment, possibly explaining partially delayed response. Response to drug and response to placebo share several common pathways, with some more affected by drug treatment. BCAAs seem implicated in mechanisms of recovery from a depressed state seemed unique to sertraline treatment.

These studies suggest that metabolic signatures of drug exposure could inform about drug mechanism of action and pathways implicated in response, and can lead to development of signatures as biomarkers of drug response phenotypes including development of side effects (18).

C. Co-Metabolism of Human and Gut Microbiome Can Inform about Pharmacokinetic (PK) Profiles of Drugs – New Types of Biomarkers—The gut microbial–mammalian metabolic axis contributes significantly to human disease, drug metabolism and response, and side effects. Studies with statin (Table I and Figure ID), acetaminophen and digoxin made clear that gut microbiome co-metabolism can impact levels of these drugs in blood and their effects (response and side effects). For review of host-gut microbiome and drug effects see (3). This suggests that metabolic signatures of host-gut microbiome co-metabolism could evolve as useful signatures for PK studies and PK modeling.

D. Pharmacometabolomics Union with Pharmacogenomics – A Systems Pharmacology Approach for Understanding Drug Effects—The pioneering work on the Pharmacometabolomics and Pharmacogenomics Research networks with SSRIs, antihypertensives and antiplatelet therapies (Table 1) (7, 9–10) has established for the first time that pharmacometabolomics data can inform and complement pharmacogenomics data, and together they can build strong foundations for systems pharmacology and enable part of the vision for Precision Medicine. Metabolic and genetic makers combined can potentially be used to develop new types of biomarkers.

Concluding Remarks

Pharmacometabolomics research can impact pharmacology, clinical pharmacology, drug discovery and development, clinical trials and Precision Medicine. Pharmacology applications include defining metabolic influences on the drug concentration reaching its target (pharmacokinetics), and influences on the target and signaling downstream of the target (pharmacodynamics). Application of metabolomic tools and data early in drug discovery and development could increase the probability of successfully selecting lead compounds for further development by providing more detailed biochemical maps of drug effects on metabolism and, potentially, correlations with outcomes. The ability to use metabolic profiles—“metabotypes”—to sub-classify patients could contribute to clinical trial design and increase success in choosing patients for trial inclusion.

Studies comparing the metabolomes of patients with different clinical characteristics (e.g., rapid vs. slow progressors) may identify new pathways for therapeutic discovery. Also comparing metabolic signatures of exposure to rapid acting drugs like ketamine for the treatment of depression with slow acting drugs like SSRIs can provide novel insights about mechanisms of recovery from a depressed state and can lead to development of more effective rapid acting therapies. Defining metabolic signatures of response to placebo and to drug and signatures for development of side effects can lead to design of confirmatory personalized trials where the drug can be targeted for a subpopulation that can benefit the most from use of that therapy. In this short review we have summarized key developments in the pharmacometabolomics field as pioneered by the Pharmacometabolomics and Pharmacogenomics Research Networks and communities. For other work and contributions please see Review (1) and citations within.

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Abbreviations

BAAT	Bile acid-COA amino acid transferase
CHOL	Cholesterol
GC-MS	gas chromatography–mass spectrometry

GCTOF	gas chromatography time-of-flight mass spectrometry
LC-MS	liquid chromatography–mass spectrometry
LDLC	low-density lipoprotein cholesterol
NIST	National Institute of Standards and Technology
NMR	nuclear magnetic resonance

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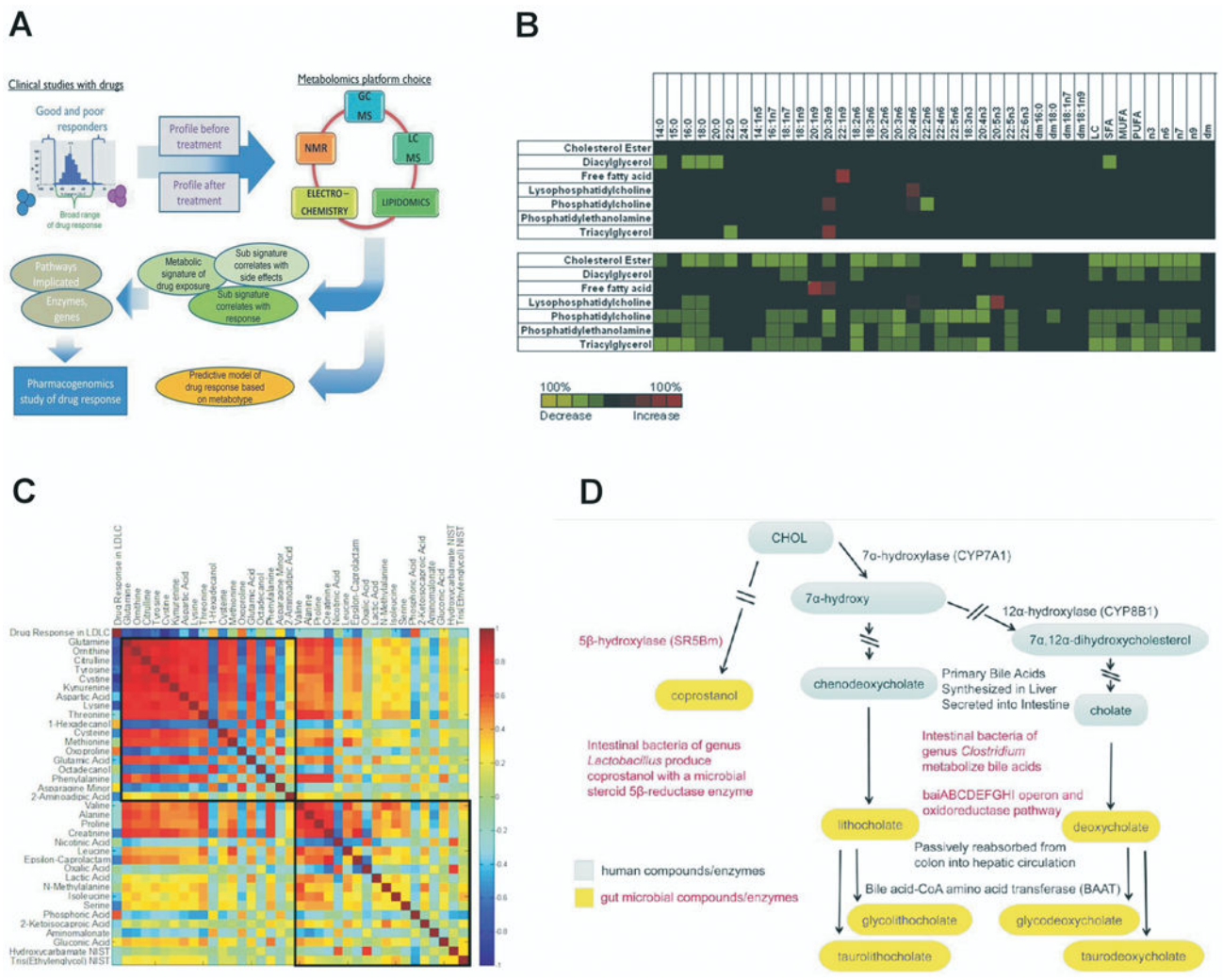

Figure 1. Exemplication of Pharmacometabolomics Approach From Studies with Simvastatin

A. Samples, typically plasma or serum, are selected from clinical studies at pre-treatment baseline and after treatment with the drug of choice. Targeted and non-targeted metabolomics platforms are used to profile these samples to test hypotheses or create new hypotheses about pathways implicated in variation in response (1). B. Heat map showing quantitative changes (nmol/g) in lipids post-treatment with simvastatin in 24 poor responders (top) and 24 good responders (bottom) (16). The column headers indicate fatty acid metabolites as they appear in each distinct lipid class (rows). Red: Lipids with percent levels significantly ($P \leq 0.05$) higher post- versus pre-treatment; Green: Lipids with significantly ($P \leq 0.05$) decreased level. Brighter square = larger difference. C. Metabolomics analysis using GCTOF platform, 100 participants treated with simvastatin (14). Correlation matrix illustrating two clusters of compounds correlated with simvastatin response in full range participants. Correlations of metabolites to drug response in Low-Density Lipoprotein Cholesterol (LDLC) are given in the first row and column, and are rescaled (divided by the largest absolute value of them) to be clearer in the map. The color scheme corresponds to correlation strength (see color bar). Red: Better response, more reduction of the metabolite; Blue: Better response, less reduction or increase of the metabolite. D. Active cholesterol

metabolites are produced by interspecies biosynthetic pathways (15). Bile acids are the main metabolites of cholesterol (CHOL). Gut bacteria of genus Lactobacillus catalyze the conversion of cholesterol metabolites to coprostanol and can limit the intestinal absorption of cholesterol. Blue ovals: Primary bile acids; Yellow ovals: secondary bile acids; Arrows broken by double lines: multiple enzymatic steps, with only the genes encoding the rate limiting enzymes listed.

Table 1

Pharmacometabolomics and Pharmacogenomics Research Networks Provide Novel Insights into Mechanisms of Action of Key Classes of Therapies

Drug Class	Key Findings and New Concepts in Clinical Pharmacology
SSRIs: escitalopram, citalopram and sertraline	Metabotype at baseline informs about treatment outcomes[4]
	Metabolic maps of SSRIs inform about delayed response[5,6]
	Metabolic maps of SSRIs reveal novel response pathways[4,5,6]
	Biochemical signatures informs about response to placebo[4,5,6]
	Pharmacometabolomics Informed Pharmacogenomics[9,10]
Lithium	Mapped novel pathways implicated in response to lithium and biochemical communication between astrocytes and neurons[11,12]
Simvastatin and pravastatin	Impact on metabolism beyond HMG-CoA reductase inhibition[13,16]
	Gut microbiome implicated in variation of response[15]
Atenolol and Hydrochlorothiazide	Metabolic maps for beta blocker atenolol reveal clear racial differences[17]
	Metabolic maps inform about development of side effects[18]
Aspirin and clopidogrel	Metabolic signatures reveal novel pathways implicated in response[7,19,20]
	Pharmacometabolomics informs pharmacogenomics[7]
Olanzapine, risperidone aripiprazole	Lipidomic maps new insights about side effects[8,21,22]