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Metabolomics in Medicinal Chemistry

Metabolomics in the pharmaceutical industry

Michael D. Reily*, Adrienne A. Tymiak

Pharmaceutical Candidate Optimization, Bristol-Myers Squibb Pharmaceutical Co., Princeton, NJ, USA

Metabolomics has roots in the pharmaceutical industry that go back nearly three decades. Initially focused on applications in toxicology and disease pathology, more recent academic and commercial efforts have helped advance metabolomics as a tool to reveal the molecular basis of biological processes and pharmacological responses to drugs. This article will discuss areas where metabolomic technologies and applications are poised to have the greatest impact in the discovery and development of pharmaceuticals.

Section editor:
Pascal de Tullio, University of Liège, Liège, Belgium.

Introduction

In the 1980's, measurement of endogenous metabolite levels in biological tissues and fluids using NMR enabled pharmaceutical applications, with a particular emphasis on the study of pathological conditions. As a result, early adoption by the industry drove advancement of this field [1–3]. Subsequent streamlining of the pharmaceutical industry led many companies to scale back on dedicated exploratory technology groups, including those supporting metabolomics. At about the same time, government funding for metabolomics research began ramping up globally and while the number of metabolomics publications coming from the industry continue to rise, they are greatly overshadowed by academic-only publications (see Fig. 1). This academic surge is significantly advancing the field, creating new interest in metabolomics as a useful tool for the elucidation of biochemical mechanisms and setting the stage for broader applications in the industry [4]. Herein, we will discuss the predominant analytical modalities, applications of highest relevance to pharmaceutical research and development, and remaining challenges for metabolomics to deliver on its full potential.

A multidisciplinary science

The mammalian metabolome is comprised of thousands of sub-kiloDalton molecules with physicochemical properties ranging from small highly polar carboxylic acids, amines and amino acids to large neutral lipids. Metabolomic studies measure this breadth of molecules and allow correlation of endogenous biochemical composition with different states of an organism to provide (1) a deeper biochemical understanding of phenotypes, (2) a facile platform for mechanistic hypothesis generation and testing, and (3) potential biomarkers for monitoring safety or efficacy. In the context of most pharmaceutical applications, it is desirable to reliably measure as many endogenous metabolites as possible to maximize the coverage of expected biochemical pathways while gaining insight into any unexpected perturbations [4]. More than just an analytical exercise, a successful metabolomic study requires close coordination amongst a diverse set of experts who are engaged at different times, but have familiarity with all aspects of the study. First, the *in vivo* study design and execution are critical to ensure collection of high quality samples at the appropriate time points, often using sophisticated equipment (e.g. specialized cages designed to provide refrigerated urine collection) [5]. Second, sample preparation requires attention to detail, to ensure that

*Corresponding author.: M.D. Reily (michael.reily@bms.com)

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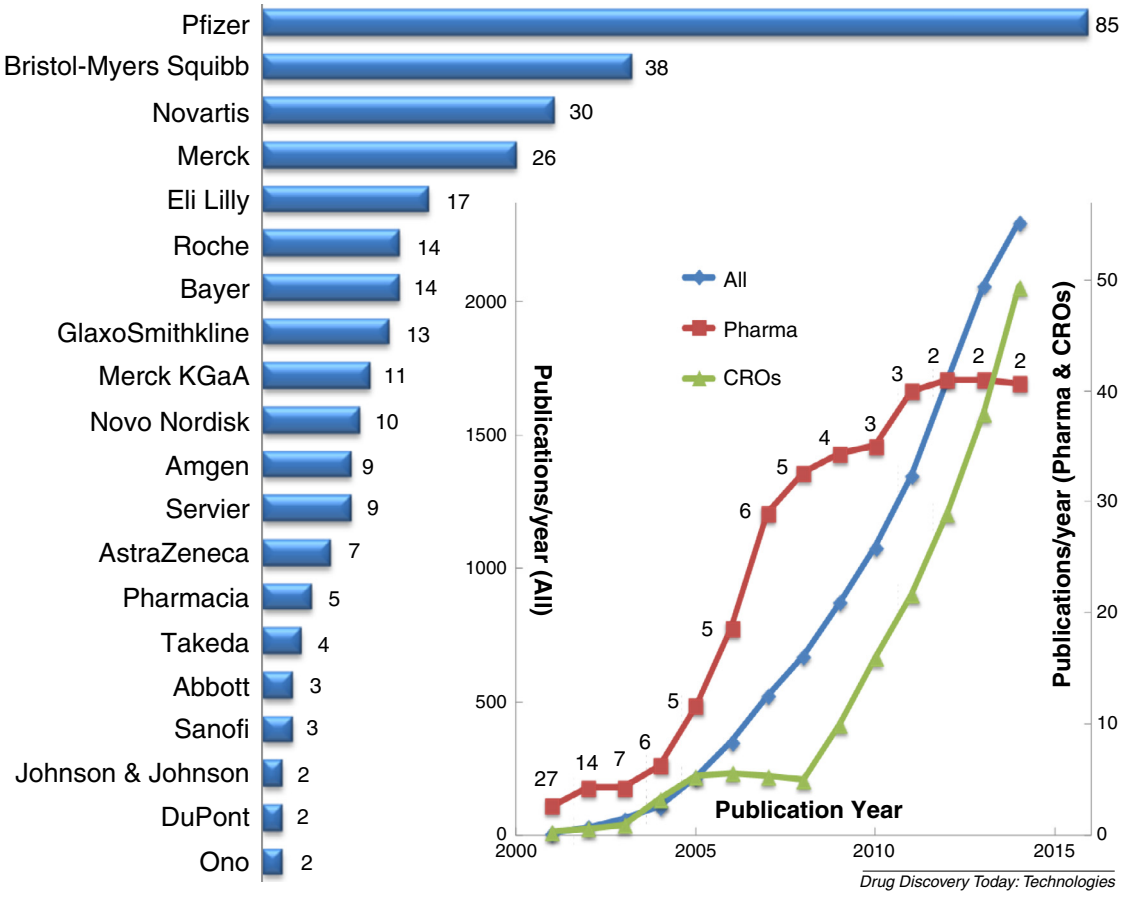

Figure 1. Metabolomics publication metrics from 1999 through 2014. The bar chart (upper left) shows the total number of publications for the largest pharmaceutical companies. The line graph (lower right) shows 3 year running averages for annual publications that list authors from all affiliations (blue line), pharmaceutical companies (red line) and contract research organizations that provide metabolomic sample analysis services (green line). Numerals over each red data point indicate the percentage of total metabolomics publications with pharmaceutical industry authorship. These data are based on the following search queries conducted in Scopus: 1) blue line 'TITLE-ABS-KEY((metabolomics OR metabonomics))'; green line '(TITLE-ABS-KEY((metabolomics OR metabonomics)) AND AFFILORG ((metabolon OR metanomics OR metabometrix OR biocrates)))'; red line and bar chart '(TITLE-ABS-KEY((metabolomics OR metabonomics)) AND AFFILORG ((glaxo OR pfizer OR roche OR nordisk OR dupont OR pharmacia OR astra OR servier OR squibb OR merck OR schering OR johnson OR lilly OR bayer OR boehringer OR sanofi OR novartis OR abbott OR amgen OR takeda OR baxter)))'.

differences between samples are biological in nature, and not due to systematic errors. To minimize the numbers of animals required in a study, peripheral biofluids such as urine, plasma or serum are used most often, but occasionally it is desirable to evaluate tissue extracts. For each target fluid or tissue, simple and robust methods must be developed and standardized procedures followed carefully in order to obtain reliable metabolomic data. Third, generating high quality data, often containing millions of data points per sample, requires a considerable time investment from analytical experts and their instruments. Fourth, these complex data sets must be analyzed in some customized manner since available software tools simply do not provide all the needed functionality. Metabolomic data analysis requires computational and programming experts with a good fundamental understanding of the analytical data and its molecular significance. Fortunately, much of this infrastructure exists within pharma and groups dedicated exclusively to metabolomics are not necessary (nor desirable), assuming that the resources are working together in an effective matrix. Finally, the end user, a biologist, toxicologist or physician, is equally important to a successful outcome, as they possess the most intimate knowledge of the system of interest and are best positioned to interpret the metabolomic results in the context of other study endpoints. While multivariate statistics has its place, we have found that a table of quantitative changes in a comprehensive and specific list of metabolites, essentially an expanded clinical chemistry panel, is often much more useful to the customer than a PCA plot.

Analytical modalities

Nuclear magnetic resonance (NMR) and mass spectrometry (MS) have emerged as the best platforms for providing metabolomic information at the molecular level. These techniques