A commentary on drug safety and genomics: Promising new agents may require expansion of guidelines for subject screening in clinical trials

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Abstract
The fatty acid amide hydrolase (FAAH) inhibitors likely represent a novel therapeutic yet complex target with the potential to impact various disease processes that present significant unmet medical needs. Despite a history of significant adverse events and still ill-defined risks associated with FAAH inactivation, potential clinical results of FAAH inhibitors for the management of human diseases suggest strongly that the research not be abandoned. In the present commentary we argue that the way to move forward safely and effectively may lie in universal expansion of clinical trials guidelines and toxicology protocols to include targeted genomic screening of clinical trial subjects. Generalization to the safety testing of many new pharmaceutical agents may be the silver lining of an otherwise dark cloud.

Keywords
Drug safety, genomics, FAAH inhibitors, clinical trial guidelines

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Kabadi et al.1 have incisively asked how biotechnology and pharmaceutical companies can better identify and mitigate the risks of new first-in-class drugs that will achieve clinical success. They go on to declare the obvious, that developing new pharmaceutical agents is a difficult and high-risk process, both clinically and economically. Regardless, it seems critical to remember that the advent of functional and readily available genomic tools provides an avenue toward gaining a comprehensive understanding of both the etiology and management of complex disease. These investigators pointed out that genomic and epigenomic tools genuinely facilitate the probing of endogenous regulatory networks that can, as one would expect, in turn, be linked to critical phenotypic outcomes.

Nowhere are the Kabadi et al.1 observations more salient than in the well-documented serious adverse events (SAEs) of the 2016 phase 1 study of BIA 10-2474, a novel orally administered fatty acid amide hydrolase (FAAH) inhibitor. Five subjects were affected and there was one death.2 It is noteworthy that FAAH inhibitors and endocannabinoids consistently appear to interact with CB1 receptors thereby eliciting analgesic and anti-inflammatory effects in animal models.3 Despite global scientific and medical scrutiny over the subsequent 5 years since the first-in-humans trial of BIA 10-2474, the catastrophic clinical effects seen remain fundamentally unexplained. It seems apparent that none of the data available to Bial and the authorities before the clinical trial, nor any of the extensive data collected by Bial or

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The prediction of toxicity of drug candidates may ultimately derive from the expansion of databases of molecular profiles for known toxicants that are used as a reference for in silico profiling of candidate molecules. By harmonizing databases and integrating genomic, epigenetic, and transcriptomic profiling of cells and tissues, it is feasible to illuminate how particular factors influence pathologic gene expression profiles. However, even after noncoding variants are connected to the regulation of a particular gene, it still may be unclear how the encoded protein or RNA from that gene influences key disease biology. Fortunately, as demonstrated in Tox21, the toolbox to fill this gap is expanding, enabled by improved human genomic annotation, high-throughput sequencing, proteomics, and bioinformatic insights.

Measuring the level of RNA transcripts from tens of thousands of different genes at once, through the use of microarrays and similar technologies, has provided the ability to monitor the expression of essentially the whole genome in the form of individual mRNA levels for a wide variety of situations and settings. These technologies have opened the door to the use of multi-variant biomarker strategies for every step in the drug discovery and development
process. Increasing use of molecular profiling is likely to lead to a shift away from the current and apparent over-reliance on in vitro monitoring of single drug-target interactions in drug discovery. Importantly, these technologies may expose off-target issues and unintended consequences during the early development of pharmaceutical agents.

As we have suggested, after isolating hits from high-throughput molecular profiling screens, it is possible to monitor the ‘on target’ and ‘off target’ effects of the compound on thousands of genes. All of this information may be carefully analyzed in METS (Microarray-Based Transcriptional Screening) platforms. In this process, insight is obtained on potential mechanism of action, selectivity, specificity, and novelty as well as information on toxicity, tumor targets, and predictions of in vivo efficacy.

We are arguing for a renewed and expanded toxicologic initiative . . . especially in light of the rapidly emerging data on polymorphism, pleiotropism, and allelic heterogeneity across individuals, that may significantly modify metabolic effects of drugs across tissues and across disease processes which themselves turn out to be remarkably heterogenous with multiple, very different sub-phenotypes that require vastly different treatment strategies. Heart failure with preserved ejection fraction is just such a collection of diseases, and the historic lack of recognition of its spectrum has likely contributed to the large number of trials with dramatically varying outcomes. 18–20

We would align ourselves with Sobreira et al. 21 in suggesting that knowledge of the genetic architecture both of metabolic pathways for drugs, and of disease-associated loci may allow us to better predict the likelihood of both therapeutic and pathological responses to pharmacologic agents.

FAAH represents a novel therapeutic yet complex target with the potential to impact various disease processes that have significant unmet medical needs. Despite the presently highlighted and ill-defined risks associated with FAAH inactivation, potential clinical results of FAAH inhibitors for the management of human diseases suggest strongly that the research not be abandoned despite the adverse events noted in the present commentary. The way to move forward safely and effectively may lie in expansion of clinical trials guidelines and toxicity protocols utilizing selected genetic screening and -omics technologies.

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