Accepted Manuscript

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PII: S2468-2020(17)30047-5

DOI: 10.1016/j.cotox.2017.06.008

Reference: COTOX 58

To appear in: *Current Opinion in Toxicology*

Received Date: 18 April 2017

Revised Date: 14 June 2017

Accepted Date: 20 June 2017

Please cite this article as: R Beger, L.-R Yu, J Daniels, W. Mattes, Exploratory Biomarkers: Analytical Approaches and their Implications, *Current Opinion in Toxicology* (2017), doi: 10.1016/j.cotox.2017.06.008.

Exploratory Biomarkers: Analytical Approaches and their Implications

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Abstract

While biomarker discovery is receiving increased attention in both drug and chemical safety assessment, a critical step is transitioning a biomarker from an experimental observation to a useful assay is that of analytical validation. This is particularly relevant as one moves from biomarker discovery using an 'omics platform to exploratory use as implemented in a more focused platform. Large scale discovery platforms for transriptomics, such as microarrays, have unique analytical considerations, different from that of more focused platforms, such as qRT-PCR. Likewise, mass spectrometry based screens of the proteome have different analytical challenges as compared to focused ELISA assays. Metabolomics experiments also require attention to analytical validation, with different considerations for quantitative or semi-quantitative assays. And while guidelines for analytical validation are still evolving, general principles certainly apply, with a solid body of literature that should be consulted by the biomarker scientist before deeming an assay as worthy of more widespread use.

Introduction

The use of biomarkers such as uroscopy is millennia old [1]. However, the term "biomarker" is relatively new, as well as a plethora of measurements, endpoints, and molecules deemed as "biomarkers"; not surprisingly an intentional effort to define terms arose and has resulted in the BEST (Biomarkers, EndpointS, and other Tools) Resource [2]. While biomarkers such as traditional clinical pathology measurements and histopathology have long been used in drug and chemical safety assessment studies [3, 4], there is considerable interest in new biomarkers that may detect certain toxicities at an earlier stage in their development and provide better assurance of safety [4-8]. Biomarkers can play a critical role in assessing environmental exposure to chemicals [9] and the impact of that exposure; and while this review will focus primarily on the use of biomarkers in pharmaceutical safety assessment, the principles and issues with analytical validation are generally applicable.

The field of biomarker discovery, development and application has been dramatically impacted by the use of 'omics technologies, i.e., those that measure the levels of hundreds to thousands of analytes simultaneously. Thus transcriptomics, proteomics, lipidomics and metabolomics measure mRNA (and micro-RNA), proteins, lipids or small molecule metabolites, respectively, *en masse* and as such cast a wide net for those molecules, i.e., potential biomarkers, whose levels are altered in response to chemical exposure or pathological state. In addition, *patterns* of such responses may be considered as biomarkers themselves. However, the characteristics of the molecules measured and the technologies used greatly determine not just their utility but also the veracity of the data generated. And while biomarkers are the subjects of books (>1300 available through Amazon!) and journals (>10), and the role of 'omics in research has been extensively reviewed, it is critical to periodically examine the strengths