Foreword

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Biomarkers in Medicine

Advancing translation of biomarkers into regulatory science

“To advance translation of more reliable biomarkers into regulatory decision-making, this issue of *Biomarkers in Medicine* solicited research articles and expert reviews in translation of biomarkers into regulatory science.”

Keywords: biomarkers • regulatory science • safety • translation

Many identified biomarkers have yet to be translated into regulatory science

The first biomarker successfully translated into regulatory decision-making at the US FDA was HER2. In 1998, the FDA approved Herceptin (trastuzumab) for treatment of breast cancer patients whose HER2 is overexpressed. Since then, translation of biomarkers into FDA regulatory decision-making has been accelerated and led to an ever increasing number of targeted therapies using biomarkers being approved, as evidenced by the fact that eight drugs (Beleodaq, Blincyto, Cardelga, Harvoni, Lynparza, Viekira Pak, Vimizim and Zykadia) for targeted therapies were approved in 2014. There are many efforts and programs at the FDA which aim to advance the translation of biomarkers into regulatory science [1–3].

Academic institutes and industry have huge investments in biomarker development. In addition, emerging technologies have been used in the discovery of biomarkers [4]. A large number of biomarkers for diagnosis and prognosis, treatment selection and dose on demand have been identified, providing more impetus for translation of biomarkers into regulatory science. Though some biomarkers have been used in the FDA's regulatory science work, many more identified biomarkers have not yet been translated into regulatory decision-making. The motivation behind this issue of *Biomarkers in Medicine* is to provide a contemporary summary of advances in translation of biomarkers into regulatory science.

MicroRNAs as noninvasive biomarkers have tremendous potential to be translated into regulatory science

MicroRNAs (abbreviated as miRNAs) are endogenous small noncoding RNAs that play regulatory roles in gene expression. Expression of some miRNAs has been found to be associated with certain diseases and drug treatment responses. Recent advances in emerging technologies, such as next-generation sequencing (NGS) technologies for measuring expression of known miRNAs and discovery of new miRNAs, have identified many miRNAs as biomarkers for diagnosis, prognosis and safety evaluation [5]. Efforts continue unabated with the aim of translating new miRNA biomarkers into regulatory science. Accordingly, this issue solicited expert reviews to shed light on recent biomarker research and to foster translation of miRNA biomarkers into regulatory science.

Drug safety is a major factor in regulation and development. This issue collected expert reviews which summarize recent efforts in the application of miRNAs as drug safety biomarkers for hepatotoxicity and cardiotoxicity testing [6–8]. Some miRNAs, such as miR-34a, miR-93–5p, miR-21 and miR-155, have demonstrated potential as biomarkers of nephrotoxicity [7,8]. Translation of miRNAs into drug safety biomarkers in regulatory science has been impeded due to concerns regarding variations among assay methods used to quantify miRNAs and lack of standards [8]. Future efforts to translate miRNA biomarkers into regulatory science for

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drug safety evaluation will focus on improvement in miRNA detection and validation of potential miRNA candidates in large cohorts.

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Drug resistance in cancer treatment is a peremptory challenge for oncologists. Studies have shown miRNAs to be potential biomarkers for identification of cancer patients who are likely resistant to specific treatment regimens [7]. Diagnosis of nonalcoholic fatty liver disease, especially determining its prognosis (from hepatic steatosis to nonalcoholic steatohepatitis), is a huge challenge in clinical practice because of the risks associated with the histologic examination method currently used. There are many studies discussing the identification of miRNAs as biomarkers for potential utilization in diagnosis of this disease. Wang *et al.* have reviewed the most recent advances in translation of miRNA biomarkers in diagnosis and prognosis of this disease [9].

More transcriptomic biomarkers are expected to be translated into regulatory science

Messenger RNAs (abbreviated as mRNAs, also known as transcripts) are the molecules that contain the information for translation of genetic information into proteins and can be measured using a variety of technologies, such as microarray and NGS [10,11]. Expression levels of sets of mRNAs are potential biomarkers that have been translated into regulatory science, such as in the US FDA approved MammaPrint®, which measures the expression of 70 genes in breast cancer patients [12] and Oncotype DX®, a 21-gene assay used in the diagnosis of node-negative breast cancer patients [13]. Many transcriptomic biomarkers have been identified and some of these are expected to be translated into regulatory science. The poor prediction performance of identified gene signatures in heterogeneous cancers has thus far hindered their translation into regulatory science. The NETBAGs algorithm, based on network analysis, was developed to overcome such obstacles [14]. Identification of transcriptomic biomarkers in traditional Chinese medicine (TCM) has gained a lot of attention in the last decade. However, few such biomarkers have been translated into regulation of TCM due to specific complications of the field, such as the difficulty of ascertaining the mechanisms of CTM. Liu *et al.* discussed the strategies that might improve translation of transcriptomic biomarkers into regulation of CTM [15]. Emerging NGS technologies promote identification of genomic biomarkers. Quality control and

standardization of NGS technologies play crucial roles in the translation of genomic biomarkers into regulatory science. The FDA-led MicroArray and Sequencing Quality Control (MAQC/SEQC) project identified quality control metrics that can be used to measure the reliability and reproducibility of NGS and microarrays, in addition to facilitating the translation of genomic biomarkers into regulatory science [16,17]. Furthermore, using multiple cancer datasets, the comparative analyses of genes as biomarkers for prognosis of cancers that are identified using microarray and NGS technologies demonstrated that biomarkers are robust to the technologies used to measure gene expression [18], alleviating the apprehension of using the huge volume of available legacy microarray data for translation of transcriptomic biomarkers into regulatory science in the NGS era.

Mechanism-based biomarkers are promising for translation into regulatory science

Mitochondria play key roles in cell life, producing essential energy for the cell in a process that involves many proteins. Toxicity due to damaged mitochondria can be detected by measuring the changes in mitochondrial genes, proteins and related metabolites. Shi *et al.* reviewed circulating mitochondrial genomic and genetic changes, proteins and metabolites in the blood as biomarkers for indication of drug-induced liver injury and discussed challenges in the translation of such biomarkers into clinical practice [19]. Compounds can bind to ionotropic GABA receptors (iGABARs) at different binding sites and thus induce epileptic seizures that affect different adverse outcome pathways (AOPs). The affected AOPs are potential biomarkers to be translated into the risk assessment of chemicals. The iGABAR antagonism-induced neurotoxicity AOPs as potential biomarkers were summarized and the challenges in translation of such biomarkers into regulatory science of chemical risk assessments were discussed [20].

Leveraging the diverse data & applying appropriate analysis methods are determinant to success of biomarkers translation

Successful translation of biomarkers into regulatory science relies on appropriate data management and mining. Du *et al.* developed HLADR, a database of human leukocyte antigens (HLAs) and their associations with idiosyncratic drug reactions observed in clinical studies [21]. HLADR is designed to enhance the discovery of HLAs as potential drug safety biomarkers and their translation into regulatory science. As most biomarkers are discovered by developing predictive models for drug efficacy and safety, the statistical analysis procedures used to construct the predictive models play crit-

ical roles in translation of biomarkers into regulatory science. Chen *et al.* reviewed the statistical methods in identification of biomarkers and discussed the statistical issues such as study designs, data analysis procedures, classification algorithms and multiple testing for validation to enhance efficiency of translating biomarkers into regulatory science [22]. NGS is an emerging technology for biomarker identification but variation exists in NGS data analysis, hindering biomarker discovery and translation. Zhao *et al.* described a NGS data analysis pipeline for identification of biomarkers for pathogen bacteria characterization and surveillance based on genetic diversity [23]. Emerging technologies have been used in biomarker identification and have generated a huge volume of diverse data [4]. Utilization of this diverse data for biomarker identification engages integration of the data at a systems biology level. Network analysis is a promising method for biomarker identification through interrogation of the interactions or associations between drugs and cell components (e.g., protein, miRNA or SNP) by integrating diverse types of data and has gained attention in the area of biomarkers translation into regulatory science [24].

More biomarkers are anticipated to be translated into regulatory science to promote precision medicine

President Obama announced the Precision Medicine Initiative in his State of the Union address early

this year. Biomarkers play a key role in the implementation of precision medicine and translation of biomarkers into regulatory science has since gained more attention from academic institutions, industry and government agency. To advance translation of biomarkers in regulatory science, the FDA has set up a biomarker qualification program to encourage specific context in the use of biomarkers [2] and proposed a conceptual framework for exploring genetic biomarkers for safety evaluation following vaccination [3]. With these under way, we expect more biomarkers to be translated into regulatory science and, ultimately, better implemented into precision medicine.

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