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Evolution of biomarkers: drug discovery to personalized medicine

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The field of biomarker research is exciting and evolving at a fast pace. According to the FDA, a biomarker is 'a characteristic that is objectively measured and evaluated as an indicator of normal biological or pathogenic processes or pharmacological responses to a therapeutic intervention' [1]. The currently used biomarkers are proteins, mRNA-expression profiling, single nucleotide polymorphisms and small molecules.

The first day of the *Biomarker World Congress 2005*, which was held 23–25 May 2005 in Philadelphia, Pennsylvania, USA, focused on updates from pharmaceutical companies on biomarker strategies and practices. Representatives from leading companies, such as Bristol-Myers Squibb, Pfizer, Johnson and Johnson, Sanofi-Aventis, Merck and Novartis Institutes for BioMedical Research, presented their biomarker-related drug discovery programs. The second day was divided into four tracks, focusing on biomarkers research in early drug development, clinical developments, molecular diagnostics and an executive summit. The final, third day of this congress was devoted to two plenary sessions on pharmacogenomics and pharmacodiagnostics followed by three concurrent post-conference focused sessions on the role of biomarker research in cancer, the central nervous system (CNS) and inflammatory diseases.

The plenary session in the first day of the congress was dedicated to sharing biomarker strategies and best practices from various pharmaceutical organizations. The speakers in this session, including Nicholas Dracopoli (Bristol-Myers Squibb), Stephen Williams (Pfizer Global Research), Hans Winkler (Johnson and Johnson), John Wagner (Merck), Jacky Vonderscher (Novartis Institute for BioMedical Research) and Robert Dix (Sanofi-Aventis), described biomarker discovery perspectives, key issues facing this emerging field and possible solutions in overcoming the potential hurdles. A few of the key issues identified in biomarker discovery programs are time, cost and availability of technology. Moreover, in the decision-making cascade of various organizations, 'time to impact' mainly influences the biomarker discovery. It was apparent from various presentations in this session that resources, long-term commitment and exploratory developmental programs could further improve the biomarker discovery initiatives. Nicholas Dracopoli emphasized how biomarkers research could provide comprehensive overview of drug action in animal models and humans, thereby impacting decision-making process, portfolio management as well as regulatory affairs. He classified the technology used to assess biomarkers into two broad groups: uniplex assays, such as single nucleotide polymorphism, quantitative polymerase chain reaction, mass spectrometry, immunoassays, bioimaging, and multiplex assays, such as whole-genome scanning, transcripts profiles and protein profiling. Describing best practices in biomarkers used in drug development, he suggested a complete integration of biomarkers' teams and compliance with changing regulatory environment based on evolutionary process of biomarkers usage in various fields.

In the second-day plenary session on 'biomarkers enable translational medicine', the role of biomarkers in translational medicine and the FDA critical path initiative in biomarker discovery were described. The first presentation entitled 'translational medicine: an interface between discovery and development' by Thorir Bjornsson (Wyeth) described biomarkers in context of translational medicine. Besides clinical endpoints, clinical and predictive model biomarkers could be used as decision-making tools in the drug development process. He described the need for the development of better biomarkers that could ultimately enhance pharmaceutical R&D capacity. The FDA's critical pathway initiative and the role of this regulatory agency in biomarker development were also unveiled by Douglas Throckmorton (Center for Drug Evaluation and Research, FDA, USA). Various regulatory issues, such as pathway to regulatory

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acceptance of biomarker and surrogates endpoint, FDA pharmacogenomics guidance and how they affect biomarkers programs, were also described in this session. Throckmorton also described the potential interactions between the FDA and various other agencies, such as academia, industry, NIH partnership and non-profit organizations.

Following the plenary sessions of this day, there were four tracks of the program. Track I included a session on 'protein biomarkers', during which the speakers discussed the current state of proteomic biomarker discovery and its role in identification of new drug targets. Several applications of protein biomarkers were described in this session. Stanley Hefta (Bristol-Myers Squibb) described the role of proteomics in ranking hepatotoxicity of various drugs undergoing clinical development for hepatic injury. Stanley Belkowski (Johnson and Johnson) discussed the role of protein biomarkers in validating model systems as well as assessing compound efficacy. Jan Schnitzer (Sidney Kimmel Cancer Center, San Diego, CA, USA) focused on the role of subtractive proteomics in tissue-specific therapeutic development in various tumors. The role of biomarkers in early efficacy and safety assessment was described by Craig Thomas (Eli Lilly), Rakesh Dixit (Merck) and Konstantin Christov (University of Illinois, Chicago, IL). Frank Dieterle (F. Hoffmann-La Roche) and Chris Beecher (Metabolon) discussed the role of various body metabolites in drug discovery as well as predicting clinical outcomes. Metabolomics, a newly emerging discipline dealing with body metabolites, could offer a platform for identifying promising drug candidates and new biomarkers in spite of the technological intricacies, such as involvement of a particular metabolite in several pathways [2]. Moreover, metabolomics is reductive in nature and currently focuses on 2400 compounds compared with 25,000 genes and 1 x 10^6 proteins and peptides in genomic and proteomic studies, respectively.

Track II sessions were oriented toward the role of biomarker discovery in facilitating and expediting clinical trials. A session on clinical utility of pharmacodynamics biomarkers focused on the role of multiplex assays in biomarker discovery. Scott Patterson (Amgen) described several examples of multiplex assays, such as detection of phospho-specific monoclonal antibodies to assess quantitatively the activation of signal transduction pathway or multiplex enzyme-linked immunosorbent assay for the detection of proteins modulated in a particular biochemical pathway, besides multi-color fluorescence activated cell sorting that could identify specific subsets of cells from whole blood. In the session on biomarker for patient selection, Jose Pineda (Washington University, St. Louis, MO) illustrated the role of clinical biomarkers in patient selection and outcome prediction in traumatic brain injury. In a joint session with Track III 'biomarkers to monitor response to therapy', Walter Carney (Bayer Healthcare) described serial monitoring of the HER-2/neu in the serum of patients with HER-2/neu-positive tumors and its utilization for early prediction of the probability of response toward anti-cancer therapeutics development.

Track III sessions were devoted to molecular diagnostics with a focused session on cancer. Because of biomarker diversity, a collaborative centralized approach among various partners involved in the biomarker field was recommended.

Track IV presentations described various strategies to improve R&D capacity and decision making as well as regulatory and proprietary issues relevant to biomarkers, including a session on pharma and biotech collaboration to further biomarker discoveries in diagnostic and drug development.

The third and final day featured two plenary sessions: pharmacogenomics in drug development and the role of pharmacodiagnostics as a potential bridging element between pharmaceutical and diagnostic industries. In the former, the relationship between the cancer treatment drug irinotecan and patients' genotype was discussed by Mark Ratain (University of Chicago, USA). A genetic variation in human *UGT1A1* gene (involved in glucuronidation) decides the predisposition of patients to side effects associated with this treatment. People possessing a variant genotype *UGT1A1*28* in the promoter region of this gene are highly prone to developing severe diarrhea and leucopenia during irinotecan therapy [3]. As such, the efficacy of this particular drug is limited in patients possessing *UGT1A1*28* genotype. A monoclonal antibody that targets the overexpression of HER2 protein in selecting breast cancer patients was also described, therefore further advancing the role of pharmacogenomics in personalized medicine, an example of which is Herceptin™ (Trastuzumab). Approximately, 20–25% breast cancer patients are HER2 positive and respond well to treatment with Herceptin™ compared with the patients negative for HER2 [4].

Post-conference focus groups

The three concurrent post-conference sessions discussed recent diagnostic and clinical advances in disease specific biomarker research, specifically cancer, CNS and inflammatory diseases.

Cancer

In the session on cancer and biomarkers, various speakers reminded the participants that cancer is a disease of genomic alterations. As such, tumor growth kinetics and molecular diagnostics are essential to support therapeutics. Besides recent advances in cancer diagnostic and therapeutic biomarkers, Daniela Gerhard (National Cancer Institute, USA) also described the efforts of the US National Cancer Institute (NCI) to integrate technologies and tools for addressing the complexity of cancer. Two of the important initiatives of the NCI are the cancer biomedical informatics grid (caBIG™), a voluntary network providing opportunity to various individuals and institutions for the sharing of data and tools, and the cancer genome anatomy project (CGAP), making available gene expression profiles for normal, pre-cancerous and cancer cells in the public domain to ultimately improve detection, diagnosis and various treatment procedures. Remaining challenges in the understanding molecular mechanisms of cancer are tumor heterogeneity at the cellular level, definition of cancer subtypes, detection of epigenetic changes and data collection and analysis.

CNS diseases

In CNS-specific biomarker research, the role of imaging in neuroscience drug development was described. The past few years have seen an immense interest in genomic and proteomic biomarkers [5], however the role of imaging

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technologies has not been highlighted. In the opening presentation, Richard Hargreaves (Merck) described the potential of imaging techniques, such as positron emission tomography (PET), as a reliable biomarker for CNS drug discovery. PET is capable of revealing the chemical functioning of the body organs *in vivo*. Other imaging technologies, such as functional magnetic resonance imaging and magnetic resonance spectroscopy, could bridge the genomics and proteomic data toward drug discovery along with serving as diagnostic biomarkers. Other presentations in this session discussed the selection of a reliable body fluid to determine biomarkers of neurological disorders. Among others, Pankaj Mehta (New York State Institute for Basic Research in Developmental Disabilities, Staten Island, NY) described the cerebrospinal fluid (CSF) as an ideal fluid for CNS biomarker discovery compared with blood sera, which can be easily modified by changes in the metabolic states, whereas CSF is shielded from such changes because of the presence of the blood–brain barrier.

Inflammatory diseases

In the inflammatory diseases post-conference session, major attention was focused on rheumatoid arthritis (RA) biomarkers. A presentation by David Boyle (University of California, San Diego, USA) on synovial biomarkers discussed various strategies to increase Phase I failure (which could be less expensive, compared with Phase II). Selection of appropriate techniques for each marker based on disease pathogenesis was considered a decisive factor in RA biomarkers' development. Ashok Amin (Virginia College of Medicine, VA, USA) presented transcriptome-based biomarker analyses describing systemic circulatory cell transcriptome signatures as representative of the RA pathophysiology. In addition to arthritis presentations, Joseph Ahearn (University of Pittsburgh, PA, USA) presented a study on biomarkers that target sepsis and proposed procalcitonin as an ideal biomarker for sepsis therapeutic development. Ahearn also presented data on the role of cell-bound complement activation products as biomarker for chronic inflammatory autoimmune disorder such as systemic lupus erythematosus or lupus pathogenesis.

Conclusions

The biomarker world congress 2005 provided an opportunity for Pharmaceutical Research and Manufacturers of America (PhRMA), regulatory agencies, academia, biotech organizations and scientists from various countries to interact and formulate good manufacturing practices in their biomarker programs. In keeping pace with this rapidly evolving field, the next Cambridge Healthtech Institute's Biomarker Series summit is scheduled 26–28 September 2005, in Philadelphia, USA. Such continued activities will play a major role in the evolution of this essential field in drug discovery and diagnostic purposes.

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