Introduction

1.1 INTRODUCTION

A biomarker may refer to a protein whose concentration refers to the severity or presence of some disease state. These biomarkers may be detectable and measurable by a variety of methods including physical examination, laboratory assays, and medical imaging. College Hill indicates that "Biomarkers are valued tools used across the biological spectrum from research to diagnostics, as indicators of normal or disease processes to assess pharmacological responses." Biomarker (biological marker) is a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic response to a therapeutic intervention. Biomarkers are proposed to measure the delivery of drugs to their intended targets, and to understand and predict pathophysiology, and how it is altered by therapy, through monitoring variables known to have chemical relevance. The intent is to use biomarkers for their predictive power to select compounds and design dosing regimens for meeting the pharmacokinetic criteria for a new drug.

Chabner (2008) has recently reviewed the challenges and advances in the use of biomarkers for clinical trials. Sheridan (2005) has indicated that protein chip companies have turned to biomarkers. Furthermore, they state that a new proteomics chip allows high-throughput protein interaction studies used in drug discovery. Baker (2005) further indicates that the "omics" revolution provides for quite a few decision-making tools. The author emphasizes that the trick lies on how to use them.

Illyin et al. (2004) indicate that the field of biomarkers has application in the diagnosis, prognosis, and in monitoring disease progression. They also assist in monitoring the responses to a therapeutic intervention, and in the delivery of personalized medicine. They further emphasize that biomarkers are involved in clinical, physiological, biochemical, developmental, morphological, and molecular measures. In drug discovery, biomarkers permit patient stratification as well as the efficacy determination of drugs. They conclude by indicating that the different technologies for data collection and analysis are critical in the different biomarker processes that involve identification, characterization, validation, and application.

Panteghini (2010) in a recent article on cardiac biomarkers emphasizes the need for a cardiac biomarker that detects the presence of myocardial damage

even before the reversible myocardial damage is induced, and thereby help identify the vulnerable patients before major events occur, permitting prior treatment. This author indicates that the increase in the blood concentration of cardiac troponins is designated as a surrogate for cardiac necrosis and myocardial infarction (MI).

Labtechnologist (2010) defines a biomarker as a "biochemical feature that either directly or indirectly provides information about a disease and its remission, and the effects of a drug compound on the disease. These biomarkers may be used to help evaluate drug therapies in clinical trials, and also serve as 'surrogate endpoints' wherein the ultimate condition in clinical trials is the patient's death if not treated effectively". Furthermore, the author adds that biomarkers are particularly useful in the efficacy of drugs for neurological diseases, for example, Alzheimer's. He recognizes that the only way to know that if a patient has Alzheimer's is to open up the brain after the patient's death. Finally, the author adds that biomarkers may also be used to minimize adverse events by monitoring the patients' response to a drug.

Nagano et al. (2010) indicate that molecular biomarkers are keys to the development of new diagnostics, protocols, and therapies. They point out that recently significant research effort has been involved in the development of biomarkers using different approaches. One of these is disease proteomics. According to them disease proteomics involves analyzing and identifying the changes in the expression pattern in the disease-related condition, that is, in basically the disease-related proteins by using two-dimensional gel electrophoresis (2D-DIGE). They emphasize on being able to pickup the right proteins that are important and significant from a large collection of disease-related proteins that have been identified. They emphasize that on using antibody proteomics one is able to identify a wide variety of disease-related proteins by 2D-DIGE. Also, this technique permits the preparation of monoclonal antibodies to these proteins using a phage antibody library.

Ramachandran (2009) has recently provided some insights into the active and high growth biomarker market. The author indicates that the biomarker definitions working group at the National Institutes of Health (NIH) initially defined, in the year 2001, a biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to therapeutic intervention". The author further indicates that biomarkers may be predictive, surrogate, and efficacy and safety. The different biomarkers may be simple molecules (glucose, cholesterol, triglycerides), macromolecules (insulin, prostate specific antigen, C-reactive protein (CRP), and hemoglobin), or complex molecules. Furthermore, the author states that the applications of biomarkers may be to (1) early disease identification, (2) help identify potential drug targets, (3) predict the response to the medication prescribed to patients, (4) help shorten the time for clinical trials, and (5) assist in the delivery of personalized medicine (since each individual is

different, biomarkers will assist the physician to prescribe the right dose for a patient).

Biomarkers are especially valuable to help prioritize drug discovery resources by enabling early proof-of-concept studies for novel therapeutic targets. There is an increased acceptance and application of biomarkers in drug discovery by pharmaceutical companies. This is primarily due to how the application of biomarkers facilitates these pharmaceutical companies to overcome the challenges posed by conventional drug discovery processes which are time-consuming and expensive. Note that high drug attrition rates, safety and efficacy concerns, and time-consuming methods have convinced the pharmaceutical sector to use biomarkers in the drug discovery process on a large scale. The Food and Drug Administration (FDA) (FDA, 2004) indicates that biomarkers are 10% more efficient in predicting drug failures and hence can save approximately $100 million and 3–4 years in each drug discovery process. In order to place this in some sort of perspective, note that it takes about $800 million and about 12–15 years to get a drug from the bench scale to the market.

In June 2006, the FDA came out with a working paper to enhance the drug development process (Goldberg and Pitts, 2010). The intent was to provide the biopharmaceutical companies with guidelines for them to bring new medicines to the market in a safer, less expensive, faster, and streamline manner. The FDA task force comprised of 25 experts from the industry, government, and scientific community. This FDA task force suggested the use of new technologies (specifically the "omics" sciences), genetic tools, and faster computers. Some of the specific suggestions included:

1. the validation of biomarkers at every stage of the regulatory process,
2. the use of validated biomarkers to assess the safety and efficacy of these specific drugs,
3. articulate the importance of congressional appropriations for biomarker research.

The report emphasizes that "biomarkers are measures of the disease progression, pharmacology, or safety that can help identify unique disease mechanisms or responses to medicine." The report also indicates that how FDA can specify how biomarkers may be used to develop drugs, biologics, and companion diagnostics. Finally, the report also suggests that a strong collaboration is required amongst the biopharmaceutical community to help validate the biomarkers.

As early as November 2001, the Tufts Center for the study of drug development indicated that the cost for developing a drug was $800 million to $1.7 billion, and the estimated time for the development was 12–15 years. The biopharmaceutical companies have a limited time to recoup these very significant amounts of money spent on R&D. They are thus spending enormous resources according to Goldman and Pitts (2006) on the applications of

biomarkers in the drug development process to help minimize the time and money spent. However, hurdles, still need to be overcome such as to predict hepatic injury (liver damage).

Among the various suggestions made by the FDA task force some are:

1. the testing and development of molecular and imaging biomarkers, and
2. specific directions for the use of biomarkers in clinical trials during drug development.

Finally, the report cautions that safety issues often come to light during clinical trials and even after marketing. These, of course, need to be avoided, or at least significantly minimized.

Turner (2012) indicates that 11% of all papers ever published on biosensors were published in 2011, and the total worldwide sales of biosensors exceeds 13 billion US dollars. He also indicates that the academic input has spawned extraordinarily.

Recently, the area of biosensor/biomarker research has expanded considerably. Recent presentations on biomarker detection have appeared in the literature including presentations at the 2010 Annual American Institute of Chemical Engineers Meeting held in Salt Lake City, Utah, November 7−12, 2010, and the 4th Biomarker Discovery and Development Conference held in San Francisco, October 20−22, 2010. Some of the presentations included:

1. Engineered knottin peptides: A new class of agents for noninvasive molecular imaging of tumor biomarkers (Moore et al., 2010). There is a critical need for noninvasive molecular imaging probes that specifically target receptors over-expressed on tumors, for earlier cancer detection and patient-specific treatment and disease management.
2. On-chip electrochemical detection of biomarkers for detection of water-borne toxins (Wilson et al., 2010).
3. Hybrid magnetic−plasmonic nanoplatelets for biomarkers (Sotiroub et al., 2010).
4. Identifying secreted biomarkers for immune evasion in cellular models of cancer (Kulkarni and Klinke, 2010). The authors attempt to analyze proteins in the bloodstream arising from the secretome of cancer cells. These proteins serve as potential noninvasive biomarkers.
5. Rational and combinatorial design of peptide affinity ligands for diagnostic assays (Chandra et al., 2010). Peptides are promising affinity ligands for the detection of proteins in biological samples. The authors used peptides to design single-step, high-sensitivity diagnostic assays for detecting s-protein as a model biomarker in human serum. The authors' intent was to develop a systematic approach for the design and discovery of peptide affinity ligands for the detection of protein biomarkers of interest.

Some of the biomarker presentations at the 4th Biomarker Discovery and Development Conference held recently in San Francisco, California from October 20−22, 2010 include:

1. Novel click chemistry-based tools for high resolution biomarker discovery (Agnew et al., 2010). These authors have developed for Molecular Probes-Life Technologies, a powerful click chemistry-based platform for applications in global biomarker discovery. For example, the authors presented a novel nascent RNA enrichment tool. This permitted global enrichment and identification of newly synthesized RNA transcripts.

2. Development of sandwich enzyme-linked immunosorbent assays (ELISAs) for potential biomarkers in pancreatic cancer (Brahmandan et al., 2010). The authors indicate that pancreatic cancer or pancreatic ductal adenocarcinoma (PDAC) is apparently one of the most deadly forms of cancer in the United States. It is also the fourth leading cause of death in men, and the fifth leading cause of death in women. The authors emphasize that biomarkers such as CA19-9 are widely used in clinics. The intent of the present study is the development of a sandwich type ELISA to help detect potential biomarkers for the early detection of PDAC.

3. Comprehensive analysis of serum peptidome using restricted access media and nanoliquid chromatography−tandem mass spectroscopy (Gil et al., 2010). These authors indicate that serum peptidome serves as a rich source of biomarkers for disease diagnosis and monitoring. These authors have developed a modular automated processing system (MAPS) for high-throughput analysis of complex biological samples.

4. The accelerated expansion of clinical use of plasma transforming growth factor beta-1 (TGFβ-1). The new paradigm of inflammation and fibrosis was given by Shoemaker et al., 2010. These authors indicate that the multifunction cytokine, TGFβ-1, regulates tissue morphogenesis and differentiation through its effects on cell proliferation, differentiation, and extracellular matrix production. Furthermore, these authors add that elevation or reduction in levels of TGFβ-1 may be connected with various disease states including cancer, diabetes, and fibrotic disease of the kidney, liver, and lung. The authors conclude by indicating that TGFβ-1 may be used as a biomarker for clinical diagnosis. It may also be used for gauging the efficacy of treatment for a diverse array of diseases and helps expand the knowledge of innate immune responses by bringing salutary new therapies to patients.

5. Antilipid response in systemic lupus erythematosus (SLE) (Jovanovic et al., 2010). These authors indicate that SLE is a chronic, multisystem, and autoimmune disorder with a broad range of clinical presentation. Several comprehensive computerized indices for measuring clinical disease activity in SLE are part of standard clinical practice. The authors emphasize that there is still a need for defining well-validated diagnostic and prognostic

biomarkers. These authors investigated lipid and autolipid antibody profiles in SLE patients using ELISA and gas chromatographic-mass spectrometry (GC−MS). The authors emphasize that reduction of lipid levels and anti-lipid IgGs at different time points would help to provide information as to the success of the treatment.

Other biomarker presentations or workshops of interest at different conferences include:

1. Translation of imaging biomarkers from research to clinical trials (van Bruggen et al., 2011).
2. Systematic biomarker data analysis workshop (Bio-IT World Conference, 2011).
3. Molecular diagnostic laboratories (MoDEL): a program to support cancer biomarker clinical assay development (Jessup et al., 2009).
4. Application of intraassay calibration curves to quantitate clinical biomarker assays (Rhyne, 2009).
5. Office of in vitro diagnostics (OIVD) outlook: biomarker-based in vitro diagnostic assays (Phillip, 2010).
6. Biomarker imaging: from molecules to man, discovery to diagnostics (Frank, 2010).
7. Circulating oncology biomarkers to guide targeted therapies: companion diagnostics for personalized medicine (Carney, 2010).
8. Establishing the interest for introducing new safety biomarkers into clinical trails (Furlong, 2011).
9. Using multiple omics principle in preclinical hepatotoxicity biomarker discovery (Salminen et al., 2011).
10. Development of biomarker panels: opportunities and challenges (Hanash, 2011).
11. Development of drug-induced vascular injury biomarkers (Brott, 2011).
12. Using mass spectrometry and immunoassays to discover and validate serum protein biomarkers for islet autoimmunity and type I diabetes (She, 2011).
13. Analyzing miR-122 as a biomarker for hepatotoxicity (Batheja, 2011).
14. Translating biomarkers from the lab to the clinic—short course (Furlong et al., 2011).

    Case studies and examples are presented related to developed biomarkers.

15. Best practices in fit-for-purpose biomarker assay validation—short course (Batheja, 2011a,b).
16. Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker of acute kidney injury and nephrotoxicity (Devrajan, 2010).
17. Biomarkers of nephrotoxicity: uses and challenges in preclinical and clinical studies (Bonventre, 2010).
18. Discovering biomarkers to predict clinical outcome (2010).

19. Those biomarkers come from biospecimens: garbage in, garbage out (Compton, 2011).
20. Oncology biomarker discovery technologies today and tomorrow (Li, 2011).
21. Development of imaging agents (Nunn, 2006).
22. Implications of pharmacogenomics for drug development (Kirk et al., 2008).
23. Pretreatment circulating vascular endothelial growth factor (VEGF) levels as a predictive biomarker of efficacy in non-small-cell lung carcinoma (NSCLC) patients treated with vandetanib (Ryan, 2010).
24. The kristen rat sarcoma (KRAS) signaling pathway biomarker in oncology: from prognostic to predictive (Patterson, 2010).
25. Incorporation of biomarkers into tarceva clinical trials (Richardson, 2010).

DePalma et al. indicate that biosensors have the potential to revolutionize the field of in vitro diagnostics. This is for human, veterinary, and food applications. The authors emphasize the role of point-of-care (POC) applications of biosensors. They have developed a sensitive magnetic bead-sensing-platform for the detection of proteins. They have presented the optimization of their magnetic immunoassay that includes surface chemistry, the blocking procedure, and the type of magnetic particles for the highly specific detection of S100ββ (a diagnostic marker for stroke and minor head injury). These authors emphasize that the use of superparamagnetic particles is an appealing alternate for the commonly used fluorescent labels, especially since they have been successfully used for the isolation of cells, proteins, and nucleic acids.

Haes et al. (2005) have developed a nanoscale optical biosensor to detect a biomarker for Alzheimer's disease from synthetic and clinical samples. These authors used localized surface plasmon resonance spectroscopy to monitor the interactions between the antigen, amyloid-β-derived diffusible ligand (ADDLs), and specific anti-ADDL antibodies. Their technique permitted the authors to determine the ADDL concentration and provided physical insights into the aggregative mechanism of this Alzheimer disease pathogen at relevant monomer concentrations.

Cassiday (2010) indicates that carbon nanotubes have been used by Professor James Rusling of the University of Connecticut to stretch the boundaries of biomarker detection. In order to move cancer detection devices closer to the clinic these authors have developed an ultrasensitive electrochemical immu-nosensor for the oral cancer biomarker, interleukin-6 (IL-6). Cassiday (2010) indicates that although existing methods can detect cancer-related biomarkers, they are not suitable for POC applications. Liquid chromatography-tandem mass spectrometry (LC−MS) proteomics analyses are labor intensive, and require expensive instrumentation. Furthermore, ELISAs (the gold standard method) are not amenable to multiplexing. This time-consuming activity increases the patient's anxiety. Rusling indicates that "what is required is a

device that could be used in a doctor's office routinely to screen people for the different types of cancer." Finally, Joseph Wang of the University of California, San Diego comments that "the excellent sensitivity of the device opens the door for the early diagnosis of cancer." This, of course, is essential for an early and timely intervention.

Cambridge Health Institute (2010) in a recent report entitled "Biomarkers in late stage clinical trials", indicates that biomarkers play a critical role in late stage clinical trials. They act as surrogate endpoints for patient monitoring and stratification. They emphasize that biomarkers may be used to lower drug attrition rates, and thereby increase the productivity and lower the cost and duration of clinical trials as indicated above. Furthermore, they help "speed up" the drug development process.

Grigsby et al. (2010) have recently designed and implemented a prototype software tool for the visualization and analysis of small molecule metabolite GC−MS and LC−MS data for biomarker discovery. The authors indicate that metabolomics is a growing field that helps characterize the metabolic profile of a specific tissue or biofluid. They further emphasize that metabolomics is an attractive approach to analyze and study the time-related quantitative multivariate metabolic responses to pathophysiological processes. These may be caused by drugs or indigenous metabolites involved in critical pathways (Reo, 2005). Reo (2005) indicates that the metabolic alterations may be expressed as a "fingerprint" of the biochemical perturbation which is characteristic of the type and target of a toxic insult or disease process. Dunn and Ellis (2005) indicate that biofluids may be obtained noninvasively (urine) or minimally invasively (blood), and they can be used in metabolomic studies. Furthermore, Wang et al. (2004) emphasize that if one were able to monitor a significant number of trace molecules, then this would be more predictive than a single biomarker. Grigsby et al. (2010) emphasize that environmental toxins and therapeutic interventions lead to nephrotoxicity. A list of metabolites indicating kidney damage would be helpful in monitoring renal conditions.

Qureshi et al. (2010) have recently developed a label-free capacitive biosensor for the sensitive detection of multiple biomarkers using gold interdigitated capacitor arrays. Their assay is able to detect a panel of disease biomarkers: CRP, tumor necrosis factor-α (TNF-α), and IL-6. Cardiovascular risk (CVR) is associated with more than one biomarker for its incidence. Hill and Martins (2006) have emphasized the development of a multianalyte immunoassay for panels of biomarkers for the diagnosis of a disease. Qureshi et al. (2010) indicate that CRP, TNF-α, and IL-6 have a strong and consistent relationship between markers of inflammation and future CVR. These authors emphasize that the early detection of a panel of biomarkers for a disease permits the prediction of the disease risk. They used a relative change in capacitive/detection properties for the detection of this panel of biomarkers. These authors also emphasize that multianalyte detection provides the advantages of shortened analysis time, simplified analytical procedure, minimal

sampling volume, improved test efficiency, and cost effectiveness when compared with parallel single-analyte assays. Stoeva et al. (2006) have used optical immunosensor arrays for the detection of multianalyte protein bio-markers. Finally, Qureshi et al. (2010) emphasize that capacitive immunoas-says may be used as an alternative to the existing immunochemical assay methods for the development of hand-held devices that may be used for POC applications.

Lin et al. (2010) have recently developed a biogenic nanoporous silica-based sensor for enhanced electrochemical detection of cardiovascular biomarker proteins. These authors indicate that proteomics research has been able to identify a number of biomarker proteins which exhibit the potential to improve disease diagnosis (Darain et al., 2004; Hahm and Lieber, 2004; Nam et al., 2003; Niwa et al., 1990). Lin et al. (2010) also indicate that the detection of multiple biomarkers provides the information to permit a robust diagnosis for a disease in any person (Abeloff et al., 2000; Chou et al., 2004; Danesh et al., 1998). They emphasize that the use of biomarkers will depend on the development of new techniques to permit the rapid and multiplexed detection of a wide range of biomarkers with high selectivity and sensitivity.

Chenevier-Gobeaux et al. (2010) have recently reviewed new biomarkers in emergency patients with cardiovascular conditions. These authors indicate that new biomarkers have changed the approach of diagnosis and treatment procedure in emergency medicine. This is especially true for cardiovascular disorders. They emphasize the integration of biomarkers in new strategies that help improve their effectiveness. Besides, the inclusion of biomarkers results in the development of tools that enhance safety and efficiency. They provide current knowledge on emergent biomarkers in emergency medicine in the field of cardiovascular diseases and infection.

Duffy et al. (2011) have recently analyzed the uses and limitations of cancer antigen 15-3 (CA15-3) as a disease biomarker for cancer. These authors indicate that CA15-3, which detects soluble forms of MUC-1 protein, is the most widely used serum marker in patients with breast cancer. It is used primarily for monitoring therapy in patients or metastatic disease. These authors emphasize that CA15-3 should be used in monitoring therapy in conjunction with diagnostic imaging, clinical history, and physical examina-tion. According to these authors CA15-3 is particularly valuable for treatment monitoring in patients who have disease that may not be evaluated using the existing radiological procedures. They emphasize that CA15-3 may also be used in postoperative surveillance of asymptomatic women who have under-gone surgery for invasive breast cancer.

Rubenstein (2007) in a report entitled "Disease-related biomarkers: their potential in patient screening, prognosis, and stratification", indicates that disease-related biomarkers are not a new phenomenon as is evidenced by blood glucose for diabetes diagnosis and management and cholesterol for cardiovascular risk. The author indicates that oncology is the most active field

for disease biomarker research and development because cancer therapy routinely provides autopsy and tissue, and also that pharmaceutical and biotechnology companies are heavily involved in cancer drug discovery. Rubenstein (2007) emphasizes that molecular biomarkers for neurological diseases such as Alzheimer's and schizophrenia are in focus since obtaining human tissue as a sample is difficult. The author emphasizes that this is essential for people who are involved in the discovery, development, validation, and commercialization of disease-related biomarkers.

Kinsinger (2010) of the National Cancer Institute (NCI)/NIH indicates the need for the development of diagnostics and for companion biomarkers. He emphasizes the importance of early detection. He indicates that one to two protein biomarkers are approved each year. He notes the three steps that are involved in the biomarker process: characterize, verify, and validate. One is able to whittle down the possible candidates from 1000s to 100s to 10s in this process. One needs to filter biomarkers before one moves them to the clinic. He emphasizes the need to develop a systematic and integrative approach.

Moore (2010) of the NCI/NIH indicates that the health costs related to cancer are around $189 million per year. She is presently the Director of the Biospecimen Research Network at NCI/NIH, and emphasizes that biospecimens are the foundations of translational research. They are at the center of the evolution of cancer research. There is a critical need for high quality specimens, and there is high emphasis on quality control.

Zheng (2010) has recently analyzed fit-for-purpose biomarker studies. He indicates that valuable biomarkers constructively aid in decision making. They emphasize that biomarker clinical trials balance right dose, right schedule, and the right patient. Two types of inputs are involved: (1) strategic input (what to test), and (2) operational input (how to test). Three simple steps are involved: sample, deliver, and assay/data. This is a multidisciplinary area which involves a multifunctional group. One needs to qualify the biomarker as a predictive or a prognostic biomarker. The authors indicate that BRAF (for melanoma trials) was examined in 500 patients. The study was still ongoing at that time. EGRF inhibitor is a predictive biomarker. The author emphasizes that informed consent is essential, and this is not a trivial process. Point-of-principle biomarkers are also involved.

Lakey (2010) has recently analyzed epigenetic biomarkers and their application in therapy selection. He indicates that 70% people benefit and 30% people do not benefit from epigenetic biomarkers. He emphasizes that people are different, but the treatments do not differ. One must take into account the molecular heterogeneity of the disease as well as the heterogeneity of the people. Lakey (2010) indicates that an epigenetic signal is a good biomarker if one can solve the spatial and temporal issues. Initially Crick had proposed the following sequence: DNA, coding, protein, metabolites. This is, however, not true now. The author is the President and Chief Financial Officer of Orion, a cancer diagnostic company. The company develops diagnostics and validation

technologies based on epigenetic differences in man. They have developed a lead breast cancer biomarker which exhibits 90% sensitivity.

Lai-Goldman (2010) in a presentation on the translation of personalized cancer diagnostics emphasizes the need for the codevelopment of biomarkers and companion diagnostics. She mentions the three criteria that are required for the development of new diagnostics:

1. unmet medical need,
2. actionable result, and
3. resources to develop evidence of clinical utility.

Also, the test should be accessible. She estimates the time required for the development of a new biomarker to be around five years.

Lakey (2010) indicates that the biomarker insulin-like growth factor 2 (IGF2) assists in the screening of colorectal cancer (CRC). The company plans to market their colon cancer risk test to the 20−40 years age group. There are about 81.6 million people in this age group. For negative patients, one may delay the test for 5−10 years. For positive patients, the author suggests that they are on a "fast track" to get CRC by the time they are 50 years old. Loss of imprinting (LOI) of IGF2 increases the risk of CRC by 21.7 times the normal. The author indicates that LOI prevalence is stable. Also, the prevalence does not increase with age. Lakey (2010) further indicates that LOI prevalence of IGF2 trials are underway. About 75,000 patients are being screened for CRC for the IGF2 biomarker.

Huey (2010) of Cambridge Biomedical Research Group in Boston in-dicates that the elevation of TGFβ-1 is linked to cancer, diabetes, etc. There is a need to develop a diagnostic assay for TGFβ-1. This is a good therapeutic and diagnostic biomarker, and is elevated in chronic fatigue patients. The author indicates that there is no true normal for TGFβ-1, since there is a wide range; besides there is age variation in TGFβ-1 levels. Huey (2010) indicates that there is a reduction in TGFβ-1 levels with the drug, Cosartan.

Kavsak (2010) indicates that a functional biomarker may be classified into three categories: preanalytical, analytical, and post analytical. An iterative technique may be involved in developing an appropriate biomarker between these three categories. The author addresses the issue of which biomarkers are important to help identify people at risk for inflammation and fibrosis. One needs to adjust for sex, age, heart failure, etc. This would assist in the unbiased selection of patients.

Brahmandan et al. (2010) indicate that there is a need to distinguish be-tween chronic pancreatic and PDAC. One may use proteomics and genomics to help discover biomarkers for PDAC. These biomarkers need to be verified and validated. The authors are developing a capture ELISA kit for DKK1. This needs to be validated before it can be tested on actual samples. They are also in the process of developing a sandwich ELISA kit for junction plakoglobin (JUP). JUP or plakoglobin is a common functional plaque protein. The

membrane-associated plaques are architectural elements in an important strategic position to influence the arrangement and function of both the cytoskeleton and the cells within the tissue. The presence of plakoglobin in demosomes and the intermediate junction suggest that it plays a central role in the structure and function of submembranous plaques.

Presently, there are no antibodies available for this and they are trying to develop antibodies for this too.

Detmers (2010) has recently analyzed "difficult" proteins, peptides, and biomarkers. The author indicates that their "Impercicer" assay is an excellent sensitivity platform when compared with other platforms. The readout system is different from ELISA. The detection is amplified by polymerase chain reaction, and is about three orders of magnitude more sensitive than ELISA. It may be used on different types of human specimens. For example, it may be used to detect biomarkers (amyloid β and tau protein) for Alzheimer's disease. In these cases the biomarker concentration is low, as well as the sample volume may be limiting (2 μl). The detection device needs to be very sensitive since the biomarkers have to cross the blood−brain barrier. The author indicates that it may be used to detect cytokines in inflammation. Patients may be stratified into low, medium, and high levels of cytokines. Thus, one may be able to give cytokine scavenging drugs. Note that ultrasensitive patient screening enhances drug responder rates. Besides, their sensitive assay may be used for infectious testing. The author emphasizes that the assays should be "drug-tolerant" to help minimize the "immunogenicity effect". Another application of their technique which Detmers (2010) suggests is doping associated with muscle growth.

Aletta (2010) has recently analyzed the application of methylarginine proteins for the treatment of autoimmune diseases such as SLE, sclerodoma, and multiple sclerosis (MS). One may be able to stratify cancer patients using a difference in methylation status. Their company is trying to develop a diagnostic for protein arginine methyltransferases (PRMT) activity. PRMTs may be linked to DNA damage responses, and may be involved in neoplastic diseases such as hormone-dependent cancers. PRMT1 is linked, this author suggests, to breast cancer, and PRMT4 is linked to prostate cancer. Aletta (2010) also suggests that these methylarginine proteins may also be linked to cardiovascular disease, hypertension, artherosclerosis, and chronic lung disease.

Vasto et al. (2010) have recently analyzed the biomarkers of ageing. These authors state that ageing is a complex process that impacts in a detrimental way in the development of different systems, and their ability to function properly. They also indicate that the rate of ageing is not uniform because of genetic heterogeneity, and the influence of environmental factors. They define ageing rate as the decline of functional capacity and stress resistance. This, they claim, is different in every individual. They define age-related biomarkers as age-related changes in body function or composition that could serve as a measure of biological age. Furthermore, these age-related biomarkers predict

the onset of age-related diseases and/or residual lifetime. The biomarkers that they put forward for analysis are based on immunosenescence, inflammatory responses, and oxidative stress. They indicate that their approach is to prevent infectious diseases and delay the onset of age-related diseases. Finally, their biomarkers help provide a better understanding of ageing as well as provide for new strategies to help counteract the ageing process.

1.2 BIOMARKER ECONOMICS AND MARKETS

Francis (2010) indicates that biomarkers are playing an important role in streamlining the drug development process. Biomarkers assist in preventing the wastage of time and money; critical resources which are in short supply, particularly for smaller companies. Biomarkers help in making decisions early of possible drug candidates that will never make it to the market by allowing research teams to find out about this as early as is possible. Francis (2010) emphasizes that biomarkers help speed up the process of getting the drug from the bench scale to the market. This very significantly assists in minimizing the costs for drug development. Thus, biomarkers assist in a faster progress for medical research.

Aarkstore enterprises (2010) emphasizes the growing recognition amongst pharmaceutical companies about the benefits of biomarkers and this has led to increasing commercial interest in this area. The authors emphasize that the potential exhibited by biomarkers in that rheumatologists may be able to predict responses of patients to expensive biological therapies based on biomarker profiles. The authors provide an identification of potentially promising biomarkers and assays. The authors emphasize that personalized medicine will eventually lead to market fragmentation. Also, an increased competition in marketed products, biomarkers, and increased market stratification will help ensure that new products get to the market and find a niche. They estimate that personalized medicine is about 5 years away for the treatment of rheumatology. They point out that cost effectiveness and health care economics are essential in this endeavor. They also emphasize the potential impact of personalized treatment approach to the treatment of rheumatology.

Pacific Biomarkers, Inc. (PBI) (2010), a provider of biomarker laboratory services to the pharmaceutical and diagnostic industries indicates that it has received an award of $244,000 for its ongoing organ injury biomarker initiative. The company indicates that their initiative met the guidelines for a qualified therapeutic discovery project and showed a reasonable potential to detect or treat chronic or acute diseases and conditions. Also, it exhibited potential to reduce the long-term care costs in the United States, and to significantly enhance the goal of curing cancer within 30 years.

PBI indicates that the aim of their program is to diagnose organ injury occurring because of specific toxic effects of drugs that are under development

and thereby prevent their approval. They emphasize that presently the costs for developing a drug are around $1 billon, and approximately 30% of all drugs do not reach the market because of drug-induced toxicity effects. PBI emphasizes that their program exhibits potential to diagnose the toxic effects that may be missed in clinical trials.

Imminst (2010) indicates that one of the best ways to look for biomarkers is by mass spectrometry. They indicate that by the year 2010, mass spectrometry research for biomarkers will exceed $75 million. In their report they list the following types of biomarkers: screening, prognostic, staging, stratification, efficacy, target, toxicity, antecedent, translational, and surrogate. The authors further emphasize the value of the biomarkers in the industry, biomarker discovery, biomarker validation, and areas of application such as cancer, CVR, diabetes, etc. The report also addresses consortia and alliances, important company profiles, and challenges.

An Austin, Texas-based biomarker company, Rules-Based Medicine, Inc. is looking for capital that can help sustain the company's rapid growth in the foreseeable future (Austin Business Journal (ABJ) (ABJ entrepreneur, 2010) entrepreneur, Inc., 2010). In order that the company could accelerate its new products to the market, the company had planned to raise $90 million on an initial public offering (IPO) according to its filing with the Securities Exchange Commission. The company had recently launched a psychiatric biomarker based on a blood test for diagnosing schizophrenia and other mental illnesses. It is also working on oncology biomarkers as well as biomarkers for other psychiatric illnesses such as depression and bipolar disorder. In the year 2009, the company was able to generate $25−30 million revenue and had 120 employees.

Rules-Based Inc. indicates that the IPO market is presently challenging since (1) investors expect higher revenues, (2) more consistent profitability, and besides, (3) there are more legal and regulatory issues. Also, an IPO depends on the industry segment. A comparison can be made between biotech and software companies. The biotech companies require a lot more time and capital to get through clinical trials and to the market. Rules-Based Inc. further adds that investors presumably prefer that companies are further along in their development process. Previously, the public market was an effective way to raise equity in a business. Nowadays, there is an increasing trend towards raising private funds. However, investors are still interested in life sciences and biotechnology companies. Finally, Rules-Based Inc. adds that presently the global molecular diagnostic market is estimated at $3.7 billion, and is estimated to grow to $6.4 billion by the year 2015. This is an increase by a factor 1.73 in five years.

Levinson (2010), founder and chairman of US Biomarkers indicates that US Biomarkers, Inc. is a formation stage company that has developed biomarkers for the early detection and diagnosis of cancer. He estimates the overall market for biomarkers to be $12 billion per year with a compounded annual growth rate (CAGR) of 15%. This is much higher than the estimate

presented at the end of the previous paragraph. He further indicates that his company is well positioned to take part in each of the following biomarker segments:

1. Biomarker discovery—$5.2 billion
2. Molecular diagnostics—$5.1 billion
3. Clinical trials—$2 billion

He indicates that the average time for the development of a biomarker should be 6−8 months presently. The company is seeking $1.1 million in initial investment for laboratory space and supplies, etc., and expects to have a revenue of $25 million in 5 years with a net income of $12 million.

Walker (2010) recently indicates that the Biomarker Factory is a company jointly owned by Duke University and Labcorp. The company coordinates medical, scientific, and commercial expertise related to biomarker development, biospecimen collection, clinical research, treatment practices, market analysis, business development, and manufacturing. He further indicates that their company is interested in diagnostics for all clinical applications, assay formats, and disease areas. For example, their work includes single biomarker assays, biomarker signatures, biomarker panels, as well as companion diagnostics for drugs.

Khetan (2007) indicates that the global biomarker market was expected to increase from $4.8 billion to $5.6 billon in the year 2007, and then to $12.8 billion by the year 2012. This is a CAGR of 18%. This author too divides the biomarker into three segments: biomarker discovery, clinical trials, and molecular diagnostics. These segments according to the author are expected to exhibit growth rates of 16.9, 23.5, and 17.5% respectively. In the year 2012, the market shares of these three segments are expected to be $5.843, 1.761, and 5.156 billion, respectively. The author emphasizes that the development of oncology biomarkers is in the forefront, followed by cardiovascular applications. This is indicated by their respective applications in clinical trials.

Markets and markets (2009) in a recent report entitled "Biomarkers-Advanced Technologies and Global Market (2009−2014)", indicates that there is a need to reduce the drug development time and cost. Besides, there are increasing concerns with regard to drug efficacy and drug safety, along with the trends towards personalized medicine. This has increased significantly the need to integrate biomarkers in the drug development process. The report emphasizes the need to obtain a better idea of the market dynamics, the competition, and the market size. Their report emphasizes biomarker tools (genomic markers and technologies, imaging biomarkers, etc.), biomarker services market (pre- and postclinical biomarker services, sample preparation), and biomarker application market (diagnosis, drug development, and discovery). The report analyzes the gaps and opportunities in the biomarker markets as well as what are the factors that are primarily responsible for the market growth.

Kirk (2008) indicates that the use of pharmacogenomics (PG_x) is almost ubiquitous in drug development especially since an increasing number of drugs are coming into the market with indicators that are related to the presence or absence of a biomarker. The authors provide a detailed review of pharmacogenomics and its tools in research, in clinical trails, and also in clinical medicine. The authors emphasize on the economic, regulatory, and technical driving forces for the adoption of pharmacogenomics in biomarker discovery. They also analyze the impediments to a more robust proliferation of these technologies in biomarker discovery and development. Nunn (2006) has also analyzed the cost of developing imaging agents for routine clinical use.

1.3 CHAPTER CONTENTS

Chapter 1 is introduction. Chapter 2 describes briefly the fractal analysis method to analyze the binding kinetics of biomarkers in solution to appropriate receptors immobilized on biosensor surfaces. The kinetics should help provide novel physical insights into the different binding and dissociation (if involved) reactions taking place on the biosensor surface.

Chapters 3 (Part I) and chapter 4 (Part II) examine and analyze the binding of the different cancer biomarkers on the different biosensor surfaces. Since this is a very active and prolific area of research, two chapters are devoted to this area of cancer biomarkers.

Chapter 5 analyzes the detection of biomarkers for MI. A very significant number of patients in the United States and worldwide suffer from this ailment. Chapter 6 analyzes the detection of biomarkers for arthritis. This includes both osteoarthritis as well as rheumatoid arthritis.

Chapter 7 discusses the detection of CVR biomarkers. The detection of glucose is a very important area of research for biosensors. Thus, two chapters, chapters 9 and 10, present the detection of glucose (biomarker for diabetes mellitus).

SLE is a very debilitating disease. Chapter 10 analyzes the detection of biomarkers for SLE using biosensors. Chapter 11 analyzes the detection of biomarkers for different nervous system diseases, such as Alzheimer's, Huntington, MS, and Parkinson's.

Chapter 12 discusses the detection of biomarkers for severe acute respiratory syndrome. Chapter 13 discusses the detection of biomarkers for different diseases such as HIV infection, hepatitis, stroke marker protein, etc.

Chapter 14 examines the markets and economics of disease-related biomarkers. This is a capstone chapter, and is very important. Especially so, since this information is scarcely presented in the open literature. One may obtain recent reports on this topic in the open market, but at a steep price of a few thousand dollars.

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