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Biomarkers in Drug Discovery and Development: From Target Identification to Drug Marketing

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ABSTRACT

The role of biomarkers in drug discovery and development has gained precedence over the years. Biomarkers play an important role in medicine and have begun to assume a greater role in drug discovery and development. Biomarkers are central to the future of medicine. By providing a measure of a biological state, they can indicate normal biological processes, pathogenic processes, or responses to an intervention or perturbation in the environment. They can be used to monitor the on-target and off-target effects of medical interventions, including treatments for disease and also in diagnostic and prognostic tests; and they can define the individuals and populations most likely to respond to therapy. At the broadest level, they can provide insight into biological pathways and networks. Biomarkers need to be taken into account while the therapeutic target is still being identified and the concept is being formulated. They need to be incorporated into a continuous cycle that takes what is learned from the discovery and development of one series of biomarkers and translates it into the next series of biomarkers. Optimum biomarker development and application requires a team approach because of the multifaceted nature of biomarker selection, validation, and application, using such techniques as pharmacoepidemiology, pharmacogenetics, pharmacogenomics, and functional proteomics; bioanalytical method development and validation; disease process and therapeutic intervention assessments; and pharmacokinetic / pharmacodynamic modeling and simulation to improve and refine drug development. The potential for biomarkers in medicine and drug development is limited by the least effective component of the processes. As scientific/regulatory foundations for biomarkers in medicine and drug development begin to be established, its applications must be effectively communicated with all of the stakeholders, including not only internal and external drug developers and regulators but also the medical community, to ensure that biomarkers are totally integrated into drug discovery and development as well as the practice of medicine.

Key Words: Biomarkers, drug development, biological processes, discovery, protein.

INTRODUCTION

In medicine, a biomarker is a term often used to refer to a protein measured in blood whose concentration reflects the severity or presence of some diseased state. By definition, it is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic response to a therapeutic intervention. More generally a biomarker is anything that can be

used as an indicator of a particular disease state or some other physiological state of an organism. A biomarker can be a substance that is introduced into an organism as means to examine organ function or other aspects of health. For example, rubidium chloride is used as a radioactive isotope to evaluate perfusions of heart muscle. It can also be a substance whose detections indicate a particular disease state, for example, the presence of an antibody may indicate an infection. More specifically, a biomarker indicates a change in expression or state of a protein that correlates with the risk or progression of a disease, or with the susceptibility of the disease to a given treatment .Biomarkers are characteristic biological properties that can be detected and measured in parts of the body like the blood or tissue.[1, 2, 3] They may indicate either normal or diseased processes in the body. Biomarkers can be specific cells, molecules or genes, gene products, enzymes o hormones. Complex organ functions or general characteristic changes in biological structures can also serve as biomarkers. For example, body temperature is well known biomarker for fever. A biomarker is a parameter that can be used to measure the progress of disease or the effects of treatment. The parameter can be chemical, physical or biological. In molecular terms biomarker is "the subset of markers that might be discovered using genomics, proteomics technologies or imaging technologies." Biomarkers play major role in medicinal biology. Biomarker brings the future things in our hand by helping in early diagnosis, disease prevention, drug target identification, drug response etc. several diseased based biomarker had been identified for many diseases such as serum LDL for cholesterol, blood pressure, P53 gene and MMPs for cancer etc. However, gene based biomarker is found to be effective and acceptable marker in the current scientific scenario. Biomarkers are being discovered and used for drug target discovery as well as decision-making during development, and are also being used clinically for disease diagnosis and treatment.[4-7] The U.S. Food and Drug Administration (FDA) have published its Critical Path Initiative and are working with experts from the academy and industry to facilitate bio-marker qualification for drug development and clinical application. In a nutshell, biomarkers are an important area for drug development and disease treatment.

CLASSIFICATION OF BIOMARKERS

Biomarkers can be classified in different ways based on different parameters. They can be classified either based on their characteristics such as imaging biomarkers or molecular biomarkers. Molecular biomarkers can be used to refer to non imaging biomarkers that have biophysical properties, which allow their measurement in biological samples (plasma, serum, cerebrospinal fluid and biopsy) and include nucleic acids-based biomarkers such as gene mutations or polymorphism and quantitative gene expression analysis, peptides, proteins, lipids metabolites, and other small molecules. Biomarkers can also be classified based on their application such as diagnostic biomarkers (i.e., cardiac troponin for the diagnosis of myocardial infarction), staging of disease biomarkers (i.e., brain natriuretic peptide for congestive heart failure), disease prognosis biomarkers (cancer biomarkers), and biomarkers for monitoring the clinical response to an intervention (HbAlc for antidiabetic treatment).[8,9] Another category of biomarkers includes those used in decision making in early drug development.[5] Biomarkers validated by genetic and molecular biology methods can be classified into three types.

Type 0 – natural history markers
Type 1 – drug activity markers
Type 2 – surrogate markers

ROLE OF BIOMARKERS IN DRUG DISCOVERY AND DEVELOPMENT

Although biomarkers have been used in drug development and treatment of disease for a long time, the identification of new predictive safety and efficacy biomarkers is expected to reduce the time and cost of drug development. In addition, the use of novel but less well-established pharmacodynamic biomarkers can further facilitate decision-making from discovery through preclinical development and into clinical trials, while rapid advances in genomics and proteonomics have increased the discovery of new biomarkers and their value in drug development and treatment of disease. Biomarkers are currently being developed to identify patients at risk for diseases and to predict potential treatment responders, adverse event occurrences, and favorable clinical outcomes for many disease states, particularly cancer. In fact biomarkers have already established important applications in the selection of therapies in which the drug targets are also the biomarkers. Biomarker measurements support target validation and proof of target, mechanism, efficacy and they are being developed first in preclinical animal models of disease.[10, 11] The journey of biomarkers in drug discovery and development is depicted in Figure 1.The majority of

biomarker research is done in clinical trials that test cancer drugs which represent the single largest therapeutic class of drugs in development.

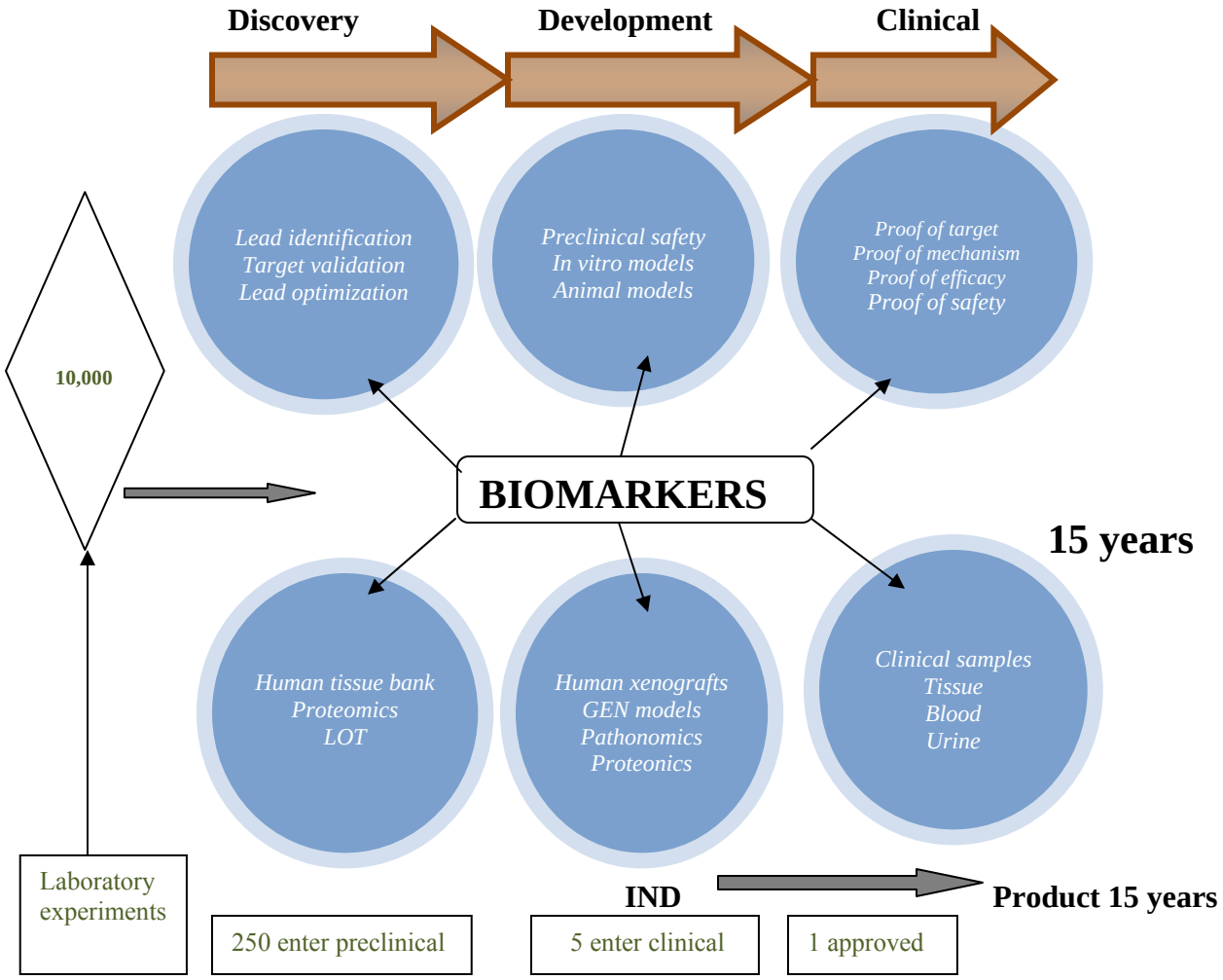

Fig 1: Role of Biomarkers in Drug discovery and development

BIOMARKERS IN ONCOLOGY DRUG DEVELOPMENT

Oncology drug development can be optimized by using a tiered set of clinical biomarkers that predict compound efficacy with increasing confidence at each level in tier. Biomarkers can be developed for application in preclinical studies, directly for use in clinical trials or, in the case of more novel markers, for translation from preclinical to clinical studies. Preclinically, biomarkers can facilitate selection of animal models and of lead compounds tested in those models. [12-14] They can demonstrate pharmacological and pharmacodynamic mechanisms-of-action in in vitro and in vivo preclinical models. Additionally, some biomarkers evaluated preclinically, such as markers that measure apoptosis or signaling pathways, can be used to mathematically model the effects of anti-cancer drug combinations to predict optimum clinical treatment regimens. Many Level-1 and Level-2 biomarkers destined for translation to the clinic are evaluated preclinically to establish that the marker is robust (as described in previous section) in a relevant model using the particular drug under development. Alternatively, biomarker assays already established for diagnostic use and treatment monitoring in humans can be modified and evaluated preclinically to assess their validity for use in clinical trials with a particular drug candidate. For example, prostatespecific antigen (PSA), a routine screen for human prostate cancer, has been adapted for monitoring the treatment response

of prostate cancer in animal. In clinical studies, biomarkers can support creative clinical development plans that optimize information gained from trials and speed drug development Traditional dose range finding clinical trials in oncology escalated up to the maximum tolerated dose (MTD), which was the intended clinical dose for cytotoxic agents. Through use of biomarkers, however, clinical trials of targeted therapies also can evaluate the minimum efficacious dose (MED), as defined by preclinical studies, and determine the optimum biological dose (OBD) based on clinical measurement of a desired biological response. New treatment regimens based on MED or OBD have fewer adverse effects in single and combination drug therapies than traditional treatment at the MTD. The pharmaceutical industry's large initiative to identify and use biomarkers that can speed and improve oncology drug development is still young. Time is needed to determine how quickly and well biomarker strategies will be able to achieve the expected increases in productivity.[15,16]

BIOMARKERS IN OTHER FIELDS

Cardiology

The best validated imaging technique for monitoring coronary atheroscelerotic disease is now intravascular ultrasonography(IVUS). IVUS, although invasive, probably surpasses conventional coronary angiography in its ability to identify atheromatous lesions in the vessel wall and then measure their distribution and size accurately. IVUS is at present being used as an end-point in several trials that study coronary artery disease regression. Few biomarkers have attained the status of surrogate endpoints for drug approval, but examples of these can be found in the cardiovascular field, in which blood pressure and cholesterol reduction are clearly linked to mortality as a result of heart attack and stroke. C-reactive peptide, an acute phase reactant, has recently been recommended as a predictive biochemical biomarker for risk of coronary disease to inform primary prevention strategies including lifestyle changes and pharmacotherapy.[17-19]

Neurology

To date, the most successful use of neuroimaging biomarker in chronic neurodegenerative disease has been Magnetic resonance Imaging (MRI) for diagnosis, prognosis and treatment of multiple sclerosis. Indeed MRI studies have been used to support the registration and labeling of interferon-1-β and have shown the benefits of early intervention. Wide ranges of imaging based biomarkers are presently being studied for Alzheimer's disease. These include volumetric MRI of whole brain or brain regions, magnetic resonance spectroscopy, single-photon-emission computed tomography (PET) and PET for amyloid plaque or microglial tracers. For Alzheimer's disease a good biomarker strategy could significantly reduce drug development timelines and optimize resources, thereby facilitating the evaluation of multiple molecules and therapeutic approaches.[19, 20]

Psychiatry

Functional models in psychiatry can use biomarkers, such as serum cortisol and adrenocorticotropic hormone, and clonidine-stimulated growth hormone release as probes for interactions with central serotonin and noradrenalin pathways. Other functional clinical experiment models, such as fear potentiated startle reflex, stimulated public speaking, and drug, lactate- or CO2- induced panic some of which include endocrine and autonomic nervous system reflex responses have also been used to discern the activity of potential anxiolytic agents.[21-23]

Depression and pain

Picture stimuli are a common way to induce emotion for experimental purposes in human subjects and it can be used in conjunction with imaging techniques including functional MRI and functional PET. Recently, hyperarousal of the amygdale in response to facial images expressing fear has been demonstrated in depressed patients. This hyperarousal was normalized by treatment with the serotonin reuptake inhibitor and antidepressant sertraline in an uncontrolled pilot study with fMRI.[24]

Clinical Biomarkers

Biomarkers have n integral role in the discovery, development, and approval of new drug products. Validation of assays for assessment of the molecular targeted effect is critical. The degree of documentation increases as the likelihood increases that the biomarker will be required to select patients for treatment or to predict benefit or possible risk. The intricacies of signaling pathways also highlight the need

for and complexity inherent in developing validated biomarkers. The FDA is becoming increasingly aware of the difficulties encountered in rapid drug development given the burgeoning amount of new scientific data, including molecular targeting. In an effort to assist companies, the FDA has issued a guidance addressing translational medicine (going from "bench to patient bedside")[25, 26]. A high degree of stringency is required before a biomarker response can be substituted for a clinical outcome and is accepted for regulatory approval. A surrogate endpoint can be defined as a laboratory measurement or a physical sign, during a clinical trial, used as a substitute for a clinically meaningful endpoint that measures changes induced by a therapy. These changes are expected to reflect changes in a clinically meaningful endpoint.[27] Reduction in cholesterol, blood glucose and viral DNA levels, as well as an increase in CD4 count, has been accepted as surrogate markers for full approval of lipid – lowering, anti diabetic, and anti HIV products respectively. Biomarkers also can be used to narrow the patient population to be treated in a clinical trial. Use of enrichment techniques can markedly reduced the sample size of the study population & also might increase the degree of response in the elevated population. [28] However, it should be noted that the FDA has not accepted changes in tumor biomarkers alone as a basis for any marketing approval of anti-cancer drugs and there have been very few "biomarkers surrogates" that have been used for full approval.

SUCCESSFUL BIOMARKERS DEVELOPMENT

Patient selection can be facilitated through the use of systems that enable selection of patient more likely to benefit from targeted therapy. Herceptest was the first such system developed. It is used to identify patients whose tumors over express Her- 2/ERB2 and, therefore, who would be more likely to respond to treatment with trastuzumab (herceptin). Her -2/neu is an example of efficacy target. Validating the target – biomarker –antibody relationship involved a great deal of effort because the initial diagnostic test was somewhat ineffective. Once the marker was validated, however, only patients whose tumours over express Her 2/neu (~ 20-25% of invasive breast cancers) were enrolled in the phase III trial. The antibodies used for the test system must work on different types of tissue. This needs to be confirmed by testing in multi-tissue. This needs to be confirmed by testing in multi-tissue arrays to make sure that background staining is not problematic. The final step is standardization of the assay to ensure consistency across laboratories. The keys to successful development of antibodies for use in patient selection are high quality –in terms of specificity, functionality and sensitivity- and standardization of reagents (no batch- to-batch variation), automated protocols and use of imaging as a means of interpreting the response.[29, 30]

The clinical development of gefitinib, an orally available epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI) is a more complex example of biomarker development. Phase I and II development of gefitinib showed dramatic and unexpected tumor regressions in ~ 10% of patients with advanced non-small-cell lung cancer but data from early –phase trial did not show a clear correlation between patient outcome and EGFR expression in archived tissue. Subsequently, however, data emerged indicating that EGFR mutations and increased gens copy number, as measured by fluorescence in situ hybridization, are associated with clinical response to genfitinib treatment. One of the challenges in the development of gefitinib was that knowledge of potential biomarkers emerged during the conduct of the pivotal trials, Indeed, increased EGFR gens copy number measured by fluorescence in situ hybridization was shown to be a prognostic biomarker for outcome after surgery in patients with non-small-cell lung cancer and subsequently shown to be predictive of response to gefitinib.[31, 32] Another example of a biomarker used as a safety target exists. Irinotecan (Campto), which is approved for treating metastatic colorectal cancer, was found to cause grade 4 neutropenia in ~8 % of the general patient population. Subsequent data have shown that uridine diphosphate glucuronosyltransferas 1A1 (UGT1A1) affects the durg's metabolism and, therefore, its toxicity profile. [33]

CONCLUSION

Biomarkers offer a means to affect rational drug design early in the development process and accelerate translational drug development from animal to man. Biomarkers represent a chance to allow proof of principle in early clinical trials in order to move rapidly to phase III and registration. Potential biomarkers can be based on biopsy material, functional imaging or proteomic approaches dependent on the kind of drug under development. They can help to define subpopulations of patients who profit or do not profit from therapy. Relevant markers may differ between the various types of targeted therapy and are under continuous development. Any biomarker used as a basis for patient selection must be validated and demonstrate excellent sensitivity and specificity as the risk of not treating patients who might benefit would

otherwise be unacceptably high. Biomarkers, placed in proper perspective, will advance both biomedical science and the pragmatic science of developing drugs that improve human health.

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