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A REVIEW ON BIOMARKER AND ITS POTENTIAL APPLICATIONS

Swarupananda Mukherjee*, Subhasis Maity, Abhishek Ghosh, Partho Pratim Biswas, Piyali Khamkat

NSHM College of Pharmaceutical Technology, 127, B.L Saha Road, Kolkata-700 053.

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***Corresponding Author**
Swarupananda Mukherjee
NSHM College of Pharmaceutical Technology, 127, B.L Saha Road, Kolkata-700 053.

ABSTRACT

Biomarkers provide a dynamic and powerful approach to understand the spectrum of various diseases including neurological diseases with application in observational and analytic epidemiology, randomized clinical trials, screening, and diagnosis. Successful implementation of biomarkers in drug development can decrease development timelines by allowing earlier go/no go decisions and increase the success of drugs in clinical trials by rationally guiding dose and indication selection. Biomarkers has gathered immense scientific as well as clinical value and is most favored and incorporated in practice of medicine. Its ability to reflect the entire spectrum of disease from the earliest manifestations to the terminal stages guides in proper treatment of the individual reduces the chances of casualties and even economic losses. This substances and their ability for the discovery of new drugs opens the door for treatment of diseases like Alzheimer's and various type of rare and deadly cancer. The abilities and potential of biomarkers allows a company for selection and production of specific drug products and also aids them for mapping out future directions. Thus overall biomarkers are a powerful tool which helps in the identification of various health effects, discovery and evaluation of various drug products and vaccines.

KEYWORDS: Biomarkers, Drug products, Mapping, epidemiology.

INTRODUCTION

Biomarkers are biochemical analytes that can be used for diagnosis, prognosis, or to evaluate response to therapeutic intervention. It could be an anatomical, histological, gene, protein/metabolite, mRNA or even a DNA sequence as to be used suitably in different field.

In practice biomarkers includes tools and technologies that can aid in understanding the prediction, cause, diagnosis, progression, regression or outcome of treatment of disease. According to National Academy of Science, Biomarkers is a xenobiotically induced variation in cellular or biochemical components or processes, structures, or functions that is measurable in a biological system. Alternatively "A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic response(s) to a therapeutic intervention.[1,2],,

Biomarkers are the substance that can be isolated from serum, urine, or other biological fluids that are useful for monitoring a particular disease state or other state for example presence of an antibody may indicate an infection. Other than this it is also put into service to signalize exposure to various environmental substances in epidemiology and toxicity. Evaluation of biomarkers requires an understanding of the differences among measurements of the cause of a disease, risk factors for outcome, and measurements of intervention effect. Advancement in the field of nanotechnology also offers the promise of miniaturized, inexpensive, flexible and robust "Plug and Play" molecular reading systems which can be effectively deployed in the field.[3] Development of novel biosensor systems which may be used to greatly aid the discovery and utilization of genetic, epigenetic or proteomic biomarkers for application in disease diagnosis is highly effective. The pubmed search till the date indicates the trend in Biomarkers research, given in fig.1.

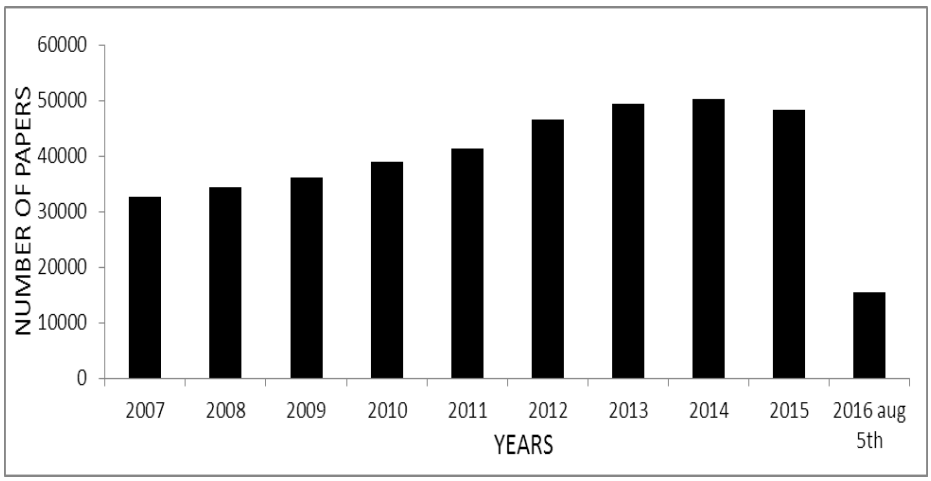

Fig 1: Trends in Biomarkers Research.

Surrogate Endpoints

Surrogate endpoints are physiological or biochemical markers that could be easily measured, and are taken as being predictive of important clinical outcomes .They are often used when

observation of clinical outcomes requires along follow up. The term surrogate should not be used in describing endpoints because these are not practically accepted .Instead descriptions of results, interpretation should be formulated in terms that designate the specific nature and category of variable assessed.[4]

General Characteristics of Biomarkers

Biomarkers could be used as indicators against various pathogenic as well biological process which could evaluated easily and further help in the development of an therapeutic regimen.

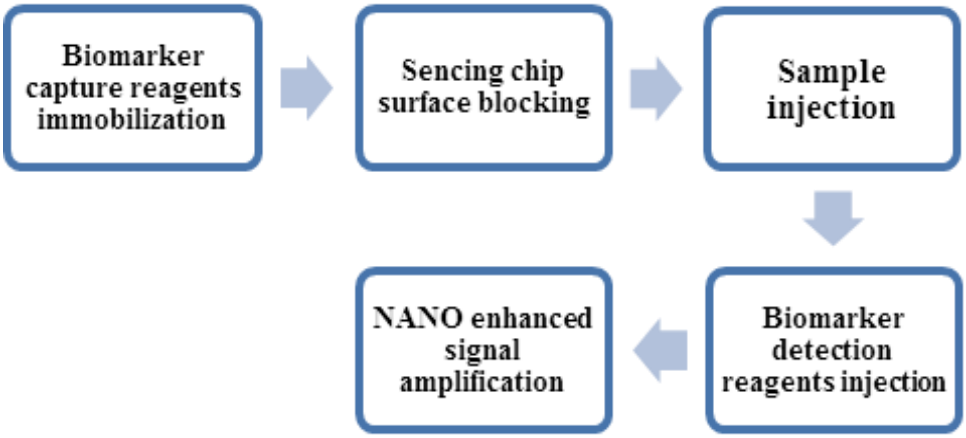

Fig 2: Utilization of nanoparticles for signal amplification.

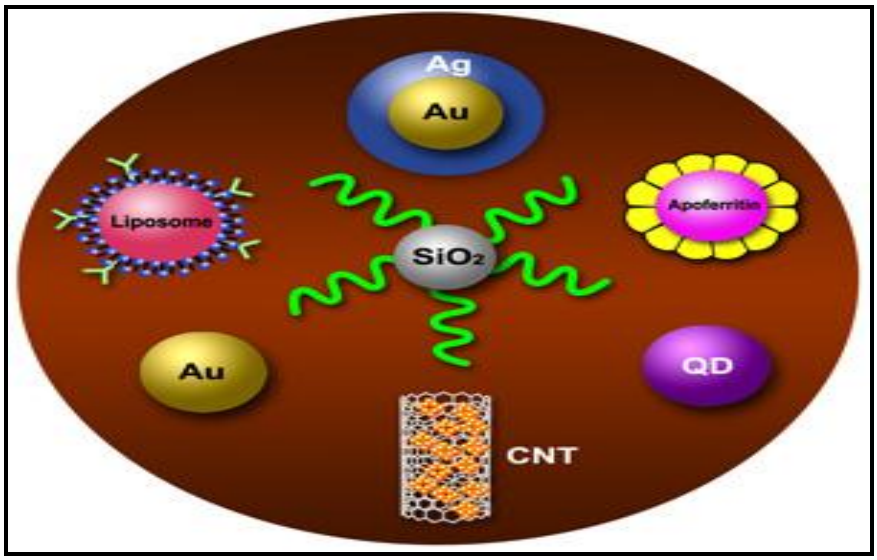

Fig 3: Materials like metal nanoparticles (gold, silver), semiconductor nanoparticles, and enzyme-loaded carbon nanotubes (CNTs) may be used to amplify biomarker signals.

Biomarkers can be characterized as a functional measure associated with a mode of protection. Biomarkers are used to identify groups of patients who respond to therapies and interventions in different ways. Biomarkers also lay stress on the early detection of disease and in the investigation of therapies/interventions aimed at reducing the risk of disease.[5]

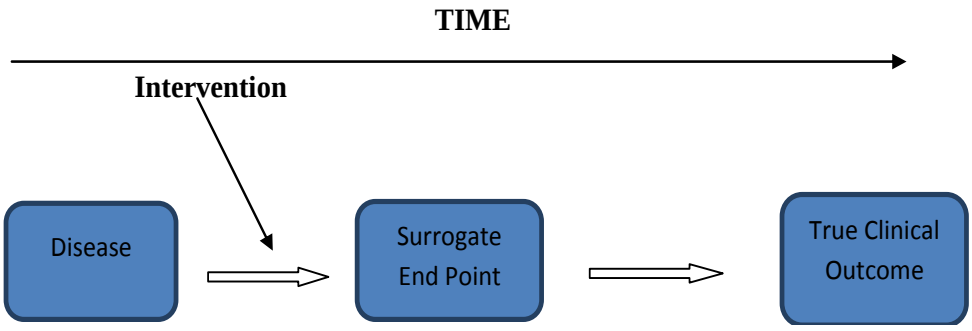

Fig 4: Surrogate endpoints used to detect true clinical outcome.

Surrogate endpoints are often used to screen candidate vaccine interventions by substituting for a primary endpoint of Phase III trials. Generally, biomarkers are used in conditions where trials, employing clinical endpoints, are not feasible or cannot be carried out efficiently and inexpensively. Trials evaluating new pneumococcal vaccines in the U.S. fall into such a category.[6,7]

Advantages of Biomarkers

These acts as powerful tools which helps in identifying the cause of the effected organ. Detection of diseases possessing multiple pathways are made easy with the aid of these tools Biomarkers are being used by increasingly by researchers associated with industry, universities, and government and have proven to be cost-effective and reliable for the purpose of monitoring, developing, and predicting efficacies for both drugs and vaccines.

Potential Disadvantages

Biomarkers are difficult to validate as well required different level of validation depending on its intended use. Thus if it's used as to reflect the success of a therapeutic regimen it should show its prominent effects.

It also increases the technical and practical challenges towards Measurement, Specifying, Over fitting, Refining. As well it loses its simplicity and also poses communication difficulties.

An example from the 1980s demonstrates the pitfalls of depending too heavily on biomarkers. In the mid-1980s two new drugs, flecainide and encainide, were introduced and incorporated with a motive to reduce ventricular arrhythmias in patients with histories of heart disease. The drugs did indeed reduce arrhythmias. A large trial, the CAST trial, was undertaken to test the efficacy of the drugs, but the trial was made stopped after a year because patients taking the drugs were found to be more than twice as likely to die as patients taking placebos. Flecainide and encainide were recalled in 1991. Their example proved that improving a biomarker does not necessarily translate into increased survival.[8-9]

Important Features of Biomarkers

Current regulations permit FDA to approve the drug on the basis of determination of its effect on a validated surrogate marker.

The FDA has also stated that it will accept immunogenicity data in lieu of traditional vaccine efficacy studies for new candidate pneumococcal vaccines.

ICH guidelines on Statistical Principles for Clinical Trials state that "In practice, the strength of the evidence for surrogacy depends upon (1) the biological plausibility of the relationship; (2) the demonstration in epidemiological studies of the prognostic value of the surrogate for the clinical outcome; and (3) evidence from clinical trials that treatment effects on the surrogate correspond to effects on the clinical outcome.[10]

Biomarkers and biomarker assays require validation. To be considered as acceptable substitutes for hard endpoints, one must have confidence that changes within a biomarker are clinically meaningful and reliably predict the effect of the treatment/intervention on the desired clinical endpoint of interest based on epidemiologic, therapeutic, pathophysiologic, pharmacologic, or other evidence.

MEASURES OF BIOMARKER TEST PERFORMANCE

Sensitivity is the ability of a test in detection of disease when it is truly present, i.e., it is the probability of a positive test result given that the patient has the disease.[11]

Specificity is the ability of a test in excluding the disease in patients, who do not have disease, i.e., it is the probability of a negative test result given that the patient does not have the disease.

Predictive value is an indication of how efficient the test is in the prediction of the true positives or true negatives, i.e., the probability that the test will provide the correct diagnosis.

The positive predictive value is the probability that a patient possess the disease given that the test results are positive.

The negative predictive value is the probability that a patient does not possess the disease or condition given that the test results are indeed negative.

A ROC curve is a plot of the sensitivity versus (1–specificity) of a diagnostic test, in which the different points on the curve, corresponds to a different cut points used to determine whether the test results are positive.

Prevalence is defined as the prior probability of the disease before the test is being performed.

The likelihood ratio is a simple measure of diagnostic accuracy, given by the ratio of the probability of the test result among those patients who truly had the disease to the probability of the same test among those patients who do not possess the disease.

Likelihood ratio (test negative) = (1–sensitivity)/specificity.

Number needed to diagnose is derived from 1/ [sensitivity–(1–specificity)], number of tests that need to be performed to obtain a positive response for the presence of disease.

Number needed to screen is defined as the number of people that need to get screened for a given duration to prevent one death or adverse event.

Clinical trials of screening: number needed to screen is calculated as the number needed to screen equals 1 divided by the absolute risk reduction.

Other trials: number needed to screen is calculated by dividing the number needed to treat for treating risk factors by the prevalence of disease that was unrecognized or untreated.

TYPES OF BIOMARKERS[12]

Biomarkers are generally classified into 3 major characteristics

Biomarkers that give information upon a disease status or risk. In TSC an electroencephalogram is often useful in the diagnosis of seizure types or in the assessment of risk of developing seizures.

Biomarkers that measures the effect of an applied drug or other intervention on a biological process. This type of biomarker does not give any information as to whether the disease is being affected, but it does show whether the drug is having its expected therapeutic activity or not.

Biomarker that measures the direct interaction of a drug with a direct molecule, or receptor. This type of biomarkers are commonly used in laboratory studies, although some compounds detected by PET scanning can be used in clinical studies

APPLICATIONS

Biomarkers in Drug Development

Imaging Biomarkers

Many newly developed biomarkers involve imaging technology. There are many advantages in imaging biomarkers. Mainly they are noninvasive, and they produce intuitive, multidimensional results. Yielding both qualitative and quantitative data, also they are that much comfortable for patients. When they are combined with other sources of information, they can be very useful to clinicians seeking to make a diagnosis.[13]

The most active area of biomarker research is Cardiac imaging. Coronary angiography, an invasive procedure requiring catheterization, has long been the gold standard for diagnosing arterial stenosis, but scientists and doctors hope to develop noninvasive techniques. Many believe that cardiac computed tomography (CT) has great potential in this area, but researchers are trying hard to overcome problems related to “calcium blooms,” a phenomenon in which calcium deposits interfere with image resolution. Other intravascular imaging techniques involving magnetic resonance imaging (MRI), optical coherence tomography (OCT), and near infrared spectroscopy are also being investigated.

Table No 1: Stages of Development using Biomarkers.

Stages of Development	Uses of Biomarkers
Pre-Discovery	Study of disease mechanism
Discovery	Define and validate drug targets Mechanism of action of drugs Establish structure–activity relationship (SAR)
Pre-clinical	Build PK/PD models Mechanism of action of drugs Safety and efficacy end points Guiding compound selection and retention
Early Clinical	Bioequivalence Dose response Mechanism of action of drugs in humans
Late Clinical	Define the target population Dose selection and optimization
Marketing – Post Marketing	Marketing - Post Marketing Monitor therapeutic response side effects

Another new imaging biomarker involves radio labeled fludeoxy glucose. Now a day the use of Positron emission tomography (PET) is to measure where in the body cells take up glucose. Tracking of glucose usually used by doctors to find sites of inflammation because macrophages there take up glucose at high levels. Tumors also take up a lot of glucose, so the imaging strategy can be used to monitor them as well. Tracking radio labeled glucose is a promising technique because it directly measures a step known to be crucial to inflammation and tumor growth.[14]

Biomarkers in Cancer

Biomarkers are used to detect and observe specific disease in the body for example cancer. Their role is to differentiate the desired cells and target them. They are also for this purpose in the form of tags. Whenever they are used to target cells in the body they can be easily identified for the presence of the tags. As cancer is developed due to the genetic mutation in the body, so specific biomarkers are used to detect that in which part of the chromosome, the mutation has occurred. The disease susceptibility can also be tested with the biomarkers. The use of biomarkers in the case of oncology, then they give many therapeutic drugs which are being used against cancer treatment. For example, a drug Herceptin or HER_2 is the first humanized antibody which is being used for the treatment of metastatic breast cancer. This drug acts as a biomarker. The main function of this drug is to block the function of the cancerous cells.

Few of the recent biomarkers being utilized for early cancer detection may be summarized as below.

Circulating DNA and RNA as possible markers in lung cancer patients

Scientist applied different studies evaluating the role of circulating nucleic acids in the blood of lung cancer patients. Despite this there is no clear concept about their possible clinical application because of the limited number of the patients, the absence or small number of controls and the lack of validated methods for detection.

Total DNA

The total amount of DNA in lung cancer patients is assessed quantitatively by different methods in a number of studies and it varies between 50% and 70%, because of the lack of sensitive methods for detection. The largest study of Sozzi et al. included 100 lung cancer patients and 100 controls of heavy smokers. The circulating amount of DNA is determined with real time PCR which led to a specificity of 95% and a sensitivity of 78%.

Circulating Gene Mutations

The most commonly investigated mutations in circulating DNA of lung cancer patients are ras and p53. The number of RAS and p53 mutations range between 0-30% and 10-30% respectively. K-ras point mutations in blood are identical to those in lung cancer tissue but are not always found despite their presence in tumor. In contrast to this p53 mutations are detected in 41% of lung cancer tissue and the identical mutations are also present in 78% in the blood of the tumor positive patients.[15]

Microsatellite Alterations

Losses of hetero zygosity and allelic shift have been the aim of investigation of different studies. DNA alterations in cancer tissue were detected in approximately 60% (range 50%-80%). The same aberrations are detected in blood of 70% (range 55% - 90%) of the patients, which proves its tumor origin. To increase the percentage of abnormal findings two to nine markers have been used. Microsatellite alterations are present in 24%-71% in the plasma of patients.

Alcohol Biomarkers in Patients Admitted for Trauma

Excessive use of alcohol can cause trauma; it complicates assessment of injury and inpatient care. Alcohol can interfere with accurate assessment of trauma in the brain or central nervous

system like head injury, degree of pain, fractures, chest and abdominal injuries. Alcohol biomarkers may give unique information and can also assist in the management of patients admitted to trauma centers. Traditional alcohol biomarkers include mean corpuscular volume, gamma glutamyl transferase, aspartate aminotransferase and alanine aminotransferase. Another biomarker is BAL which is used by law enforcement agencies, transplant programs, alcohol and drug treatment programs and some trauma centers.

Biomarkers in Alzheimer's disease

Biomarkers can be the best ever technology to treat the Alzheimer's disease. The major problem of Alzheimer's disease is that symptoms of disease appear to develop only after substantial 4cell loss has occurred in brain. Effective biomarker tests can be used to manage such dangerous damage occurring. This will be particularly important once a cure or more effective medications become available. Medications at present for Alzheimer's disease can only provide some short term improvements in cognitive function. Current biomarkers for Alzheimer's disease include.

Beta-amyloid measured in cerebrospinal fluid

Tau protein measured in cerebrospinal fluid

Neural thread protein/AD7C-NTP measured in cerebrospinal fluid and in urine.

In people with Alzheimer's disease their cerebrospinal fluid contains a reduced level of 42-amio-acid beta-amyloid and an increase in tau protein.

Biomarkers of Epilepsies[16]

Epilepsy is the most common serious primary disease of the brain. Biomarkers for epileptogenicity, the presence and severity of an epilepsy condition, or epileptogenesis, the development and progression of an epilepsy condition. The identification of reliable biomarkers would greatly facilitate differential diagnosis, eliminate the current trial-and-error approach to pharmacotherapy, facilitate presurgical evaluation, and greatly improve the cost–effectiveness of drug discovery and clinical trials of agents designed to treat, prevent and cure epilepsy. Identification of reliable biomarkers of epileptogenicity and epileptogenesis for research and clinical applications is a high-priority goal for the epilepsy community. Recent advances in electrophysiology, neuroimaging, molecular biology and genetics promise to reveal clinically useful biomarkers for epilepsy in the near future.

CONCLUSION

Many studies using biomarkers never achieve their full potential because of the failure to adhere to the same rules that would apply for the use of variables that are not biological. The development of any biomarker should precede or go in parallel with the standard design of any epidemiological project or clinical trial. In forming the laboratory component, pilot studies must be completed to determine accuracy, reliability, interpretability, and feasibility.

Future Application

A large concerted effort is required to advance the field of biomarker discovery. Most current biomarkers do not satisfy the required characteristics for use among the spectrum of diseases. Validation of new biomarkers is necessary. Generation of prospective data will be necessary for validation and demonstration of clinical utility. High-throughput technologies have begun to define disease processes and other biological processes with molecular biology detail and thus offer the potential to identify and characterize novel biomarkers. Molecular biology is now seen as encouraging more 'personalized medicine' – the closer alignment of biological information (derived from molecular diagnostics) and therapy selection. Well designed efforts will be needed to develop general knowledge about the molecular history of diseases, to keep up with the progress with biomarkers development. The evolution of molecular medicine, coupled with the discovery and clinical application of new biomarkers, will play a significant role in reshaping medicine as a science.

Science in India could make a significant impact on the global scene if scientists and policy makers could agree to dedicate sufficient time and resources to the field of biomarkers. This should be much beyond task-force and excellence initiatives, and should be output-driven in a defined time line.

New Ways of Working

Integrating biomarkers into drug discovery and development presents a number of challenges to traditional approaches. For a diagnostic to be co-developed with a drug requires adaptations of the clinical programme and the design of individual trials to incorporate the diagnostic development alongside the drug development. On an organizational level, one feature of applying biomarkers is the need for multidisciplinary teams and greater levels of integrated working across different disciplines, bringing together biological, numerical and analytical skills. Another feature is the blurring of the traditional boundary between discovery and development, requiring the sharing of information both up and down the pipeline.

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