J. Biol. Engg. Res. & Rev. 2014

Journal of Biological Engineering Research and Review | JBERR |

E-ISSN: 2349-3232

www.biologicalengineering.in

REVIEW PAPER OPEN ACCESS

BIOMARKERS GENESIS AND THEIR PERSPECTIVES

R.K. Saxena[1]* and D.V. Rai[2]

[1]Indian Institute of Technology, New Delhi

[2]Shobhit University, Gangoh, Saharanpur, UP

***Email: rksaxena369@gmail.com**

RECEIVED: 07/01/2014 ***REVISED: 30/03/2014*** ***ACCEPTED: 09/06/2014***

ABSTRACT

Biomarkers are an index develops in living systems before/during pathophysiological situations. Their elevation or reduction can provide the status of diseases and can help in the development of therapeutics for ailment at initial level for the alleviation of etiology of disease. A particular type of the physical characteristics generated in living system can be used to measure or indicate the etiopathological nature of development, effects or progress of a disease, illness or abnormal or pathological conditions. A distinct types of biochemical, genetic or molecular characteristic or substance or indices i.e. an indicator of a particular biological condition or process. Disease biomarkers have been used in several clinical areas, including oncology, metabolic disorders, neurological disease and immune systems malfunctioning. In recent years because of the progress of analysis technology (Biomarker system) several new biomarkers continue to be devised and used as diagnostic, predictive, prognostic, and toxic marker. In drug development area, biomarkers are used as surrogate endpoint to substitute for a clinical endpoint and needed for rational drug development.

Keywords: Biomarker, Etiopathological, Biomarker system, Drug development, Surrogate endpoint

Biomarkers are biological materials in living systems and its characteristic in the body fluids provide indication of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention and can be measured and evaluated. Biomarkers are immensely popular for the assessment of diseases/disabilities, diagnosis, prognosis, and selection of memory and targeted therapies. Their use is extremely diverse, ranging from pharmaco-dynamics to treatment monitoring. A wide range of biomarkers are available and every individual biological system (for example the cardiovascular system, metabolic system or the immune system) has its own specific biomarkers. Many of these biomarkers are relatively easy to measure and form part of routine medical examinations. For example, a general health check may include assessment of blood pressure, heart rate, cholesterol, triglycerides and fasting glucose levels. Body measurements such as weight, body mass index (BMI), and waist-to-hip ratio are routinely used for assessing conditions such as obesity and metabolic disorders.

Biomarkers use has long history, since 14th century or earlier, uroscopy i.e. examining a patient's urine for signs of disease, medical practitioners used to examine regularly the color and sediment in patient's urine and make a diagnosis based on what they observed in urine

evaluation. . Today, spirometry procedure is used to measure lung function and blood pressure indices are used cardiovascular health or blood glucose level for diabetes. Also, biomarkers are useful at the 'bedside' health of diseased person; biomarkers have already proved their worth at the 'bench' as well. Biomarkers are the measures used to perform a clinical assessment such as blood pressure or cholesterol level and are used to monitor and predict health states in individuals or across populations so that appropriate therapeutic intervention can be planned. Biomarkers may be used alone or in combination to assess the health or disease state of an individual [1].

CHARACTERISTICS OF AN IDEAL BIOMARKER

The ideal biomarker is one through which the disease comes about or through which an intervention alters the disease. For example, the serum cholesterol concentration should be an excellent diagnostic marker for cardiovascular disease; however, there is no clear cut-off point, and only about 10% of those who are going to have a stroke or heart attack have a serum cholesterol concentration above the reference range. But even if cholesterol is not a good diagnostic marker, it can still be used as a marker of therapeutic response to cholesterol lowering drugs [2].

An ideal biomarker has certain characteristics that make it appropriate for checking a particular disease condition. Generally, an ideal marker should have the following features:

1. Safe and easy to measure
2. Cost effectiveness for follow up
3. Tissue based drug delivery treatment
4. Balance across gender and ethnic situations.

CONTRIBUTIONS OF VALID BIOMARKERS TO CLINICAL RESEARCH [3]

1. Delineation of events between exposure and disease
2. Establishment of dose–response
3. Identification of early events in the natural history
4. Identification of mechanisms by which exposure and disease are related
5. Reduction in misclassification of exposures or risk factors and disease
6. Establishment of variability and effect modification
7. Enhanced individual and group risk assessments

TYPES OF BIOMARKERS

There are two major types of biomarkers: biomarkers of exposure, which are used in risk prediction, and biomarkers of disease, which are used in screening and diagnosis and monitoring of disease progression. Biomarkers used in risk prediction, in screening, and as diagnostic tests are well established, and they offer distinct and obvious advantages. The classification of many neurological diseases is based on either standardized clinical criteria or histological diagnoses. Biomarkers also have the potential to identify neurological disease at an early stage, to provide a method for homogeneous classification of a disease, and to extend our knowledgebase concerning the underlying disease pathogenesis. These advantages have direct application to all types of clinical investigation, from clinical trials to observational studies in epidemiology. In epidemiological (or quasi-experimental) investigations, biomarkers improve validity while reducing bias in the measurement of exposures (or risk factors) for neurological disease. Rather than relying on a history of exposure to a putative risk factor, direct measurement of the level of exposure or the chromosomal alteration resulting from the exposure lessens the possibility of misclassification of exposure. Such misclassifications not only produce inaccurate and deceptive results but also reduce the power of studies to detect health effects. Thus, the use of biomarkers improves the sensitivity and specificity of the measurement of the exposures or risk factors. Molecular biomarkers have the additional potential to identify individuals susceptible to disease.6 Molecular genetics have already had an impact on neurological practice, leading to improved diagnosis. Classification of populations in terms of the degree of susceptibility on the basis of such biomarkers produces greater accuracy than relying on historical definitions of susceptibility [4, 5]. For example, a biomarker will allow the stratification of a population on the basis of a specific

"genotype" associated with a disease rather than relying on a report of the "family history" of the disease. The ability to quantify "susceptibility" in this way can be an extremely important method for estimating disease risk among various populations [6].

USES OF BIOMARKERS

Biomarkers can be used for the prediction of complicated and serious illnesses such as diabetes and cardiovascular disease [7]. Each individual biomarker indicates whether there is a disease or health state and can be combined to provide a detailed picture of how healthy a person is and whether or not a diagnosis needs to be made. The methodology of biomarkers in diagnosing the disease has been used for the detection, screening, diagnosis, treatment and monitoring of cancer. Traditionally, anti-cancer drugs were agents that killed both cancer cells and healthy cells. However, more targeted therapies have now been developed that can be directed to kill cancer cells only, while sparing healthy cells. The assessment of a typical biomarker in cancer helps in the development of therapies that can target the biomarker. This can minimize the risk of toxicity and reduce the cost of treatment. In cancer research, genetic studies are valuable because genetic abnormalities so often underlie the development of cancer. Certain DNA or RNA markers may therefore help in the detection and treatment of specific cancers [8].

Recently, researchers from Europe have identified four biomarkers by using high-throughput molecular profiling (NMR Spectroscopy). The four circulating biomarkers namely—alpha-1-acid glycoprotein, albumin, VLDL particle size, and citrate were identified. All four biomarkers were predictive of death from cancer and nonvascular causes in addition to cardiovascular mortality, and may therefore indicate novel relationships between systemic biomarkers and diverse morbidities. This was done after screening blood samples from over 17,345 persons for over 100 different biomolecules. The health status of these study volunteers was followed for several years. The researchers looked for measurements in the blood of elderly population who had died within the following 5 years and their after blood samples were taken during hospitalization and observed that there are four biomarkers changed considerably before their death [9].

Biomarkers have been found to play a crucial role in improving the drug development process as well as in the larger biomedical research enterprise. Understanding the relationship between measurable biological processes and clinical outcomes is vital to expanding our arsenal of treatments for all diseases, and for deepening our understanding of normal, healthy physiology. Since 1980, it was found that the necessity of using biomarkers as surrogate endpoint in large trials of major diseases, such as cancer and heart disease, has been widely discussed. Several agencies promote the use of biomarkers in basic and clinical research, as well as research on potential new biomarkers to use as surrogates in future trials. However, for all their potential to do well for speedy development of drug, to reduce exposure to ineffective experimental treatments and some times biomarkers present substantial risks when drug trial specialists gets confuse biomarkers with clinical endpoints.

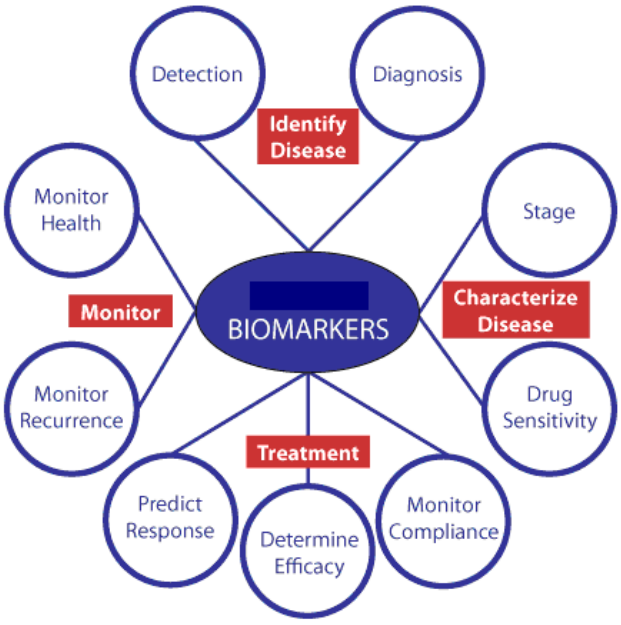

Fig.:1 Uses of Biomarkers

Biomarkers can provide definite replacements for clinical relevant endpoints, when trial specialist completely understand the normal physiology of a biological process, the pathophysiology of that process in the disease state, and effects of an intervention by pharmacological, device, or otherwise during on these processes. Since we rarely understand the full picture of those types of processes, since

there are always more details we don't know or understand biomarkers as surrogate endpoints need constant reevaluation. Studies using biomarkers should always have as ultimate measures clinical outcomes, at least for retrospective analysis of biomarker correlation success. Without continual reevaluation of the relationship between surrogate endpoints and true clinical endpoints, we risk again approving whole classes of drugs that either have no additional benefit or, worse, that harm patients [10].

A surrogate endpoint has been defined as a biomarker intended to substitute for a clinical endpoint', the latter being 'a characteristic or variable that reflects how a patient feels, functions, or survives. So, what is a biomarker? Well, that has been defined as 'a characteristic that is objectively measured and evaluated as an indication of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. Marker marks can be clearly defined i.e. intrinsic or extrinsic. The categories of biomarkers can be further subdivided according to whether the markers are being used for diagnosis, staging, or monitoring of disease or for determining its response to therapy [11].

Biomarkers are often cheaper and easier to measure than 'true' endpoints. For example, it is easier to measure a patient's blood pressure than to use echocardiography to measure left ventricular function, and it is much easier to do echocardiography than to measure morbidity and mortality from hypertension in the long term. Biomarkers can also be measured more quickly and earlier. Blood pressure can be measured today, whereas it takes several years to collect mortality data. In clinical trials the use of biomarkers leads to smaller sample sizes. For example, to determine the effect of a new drug on blood pressure a relatively small sample size of say 100–200 patients would be needed and the trial would be relatively quick with in years. In order to study the prevention of deaths from strokes, a large and study group will be needed and the clinical trial should done be for several years for arriving for definite conclusions. Also, there may also be ethical clearance and problems associated with measuring true endpoints. Severe liver injury/damage due to paracetamol (N-acetyl-p-aminophenol) overdose and it is unethical to wait for evidence of before deciding whether or not to treat a patient; instead a pharmacological biomarker i.e. the plasma paracetamol concentration should be used to predict (biomarker) whether treatment is required or not.

There are many links in the chain of events during onset of disease i.e. develops due to the pathogenesis of a disease and appears as its clinical manifestations; biomarkers can be used at any point in the chain, at the molecular, cellular, or organ levels. Likewise, a therapy might be developed to attack any one of these links, in order to try to manipulate the disease, symptomatically or therapeutically. Any measurement short of the actual outcome could be regarded as a surrogate endpoint biomarker. However, although all surrogate endpoints are biomarkers, not all biomarkers are useful surrogate endpoints.

Other usefulness of biomarkers is that they are not directly related to the clinical endpoint, but are affected in parallel with the disease. In some cases they are good diagnostic markers but sometimes they are not good markers in progress of disease (e.g. prostate specific antigen in prostatic cancer) or conversely they may be good markers in the progress but not helpful diagnostically (for example carcinoembryonic antigen in ovarian carcinoma).

Surrogate endpoints and their mode of action

Surrogate endpoints of diseases are very useful, when the pathophysiology of the disease and the mechanism of action of the intervention are thoroughly understood; otherwise, it may provide erroneous results. It is well known that smoking causes lung cancer, and a trial of the benefit of education in preventing lung cancer might use smoking as a surrogate endpoint rather than the occurrence of the cancer itself. On the other hand, if chemotherapy is used as a measure for treating lung cancer, smoking could not be used as a surrogate endpoint. This is under stable, also warns us for the possibility of similar but less noticeable examples, in which the mechanisms are not understood. Ventricular arrhythmias causes sudden death and antiarrhythmic drugs prevent ventricular arrhythmias. It was therefore expected that antiarrhythmic drugs would prevent sudden death. In fact, in the Cardiac Arrhythmia Suppression Trial, Class I antiarrhythmic drugs increased sudden death significantly in patients

with asymptomatic ventricular arrhythmias after a myocardial infarction and the trial was stopped prematurely. The hypothesis was wrong. Another good example is Enalapril and vasodilators, such as hydralazine and isosorbide, whose haemo-dynamic effects and effects on mortality associated with heart failure, are dissociated. Vasodilators improved exercise capacity and improved left ventricular function to a greater extent than enalapril. However, enalapril reduced mortality significantly more than vasodilators. So in this case haemodynamic effects are not a good surrogate.

Patients with asthma feel breathless and when they have a low peak expiratory flow rate (PEFR). However, it is observed that different anti asthmatic drugs produced different reactions between PEFR and breathlessness for example patients taking beclomethasone did not feel as breathless as those taking theophylline for a given PEFR. So what should the surrogate marker be – the 'hard' endpoint of peak flow or the 'soft' marker of how the patients felt? This also raises the question of whether more than one surrogate endpoint should be used in clinical trials.

Interrelated factors can nullify the value of surrogate endpoints. For example, serum T3 is used as a marker of the tissue damage that thyroid hormone causes in patients with hyperthyroidism. However, its usefulness is blunted in patients taking amiodarone, which interferes with the conversion of T4 to T3 without necessarily altering thyroid function.

Statistical problems with surrogate endpoints [12]. Statistically, surrogate endpoint has been defined as 'a response variable for which a test of the null hypothesis is not having any relationship to the treatment groups, also under comparison it is a valid test of the corresponding null hypothesis based on the true endpoint'. Often the surrogate endpoint is used as an entry criterion in clinical trials, and it is important to be aware that this can lead to statistical problems. It introduces heterogeneous variance and the problem of regression to the mean. If someone is entered into a trial on the basis of an abnormal surrogate marker and then receives no treatment, the surrogate endpoint will still improve, simply because of the statistical variation in the measurement of variables. This reduces the power of a study. There is also a high likelihood of missing data when surrogate endpoints are used. It is observed that including a small sample size when using a surrogate endpoint may also mean that a study is not big enough to detect adverse effects of drugs.

New biomarkers

Several biomarkers have been used since long time. Biomarkers are used as a measuring index for the time of relapse of cancer in a patient with cancer as a surrogate endpoint for survival time. In medical science ocular pressure measurement is used as an index for assessment of loss of vision in patients with glaucoma [13]. Biomarkers are used to predict the stage of disease (for example the number of lymph nodes affected by cancer), in diagnosis (for example serum T3, electrocardiography, and auto-antibodies), and to monitor the progress of a disease or its treatment (for example, blood glucose concentration, blood pressure, and FEV1).

The search for useful biomarkers for therapeutics and diagnosis is a continuous process. Several new biomarkers have been invented and investigated for neuropsychological, neurophysiological, and neuroendocrine tests and motor skills in healthy subjects. A useful biomarker should meet the following requirements: a consistent response across studies and drugs; a clear response of the biomarker to a therapeutic dose; a dose–response relationship; a plausible relationship between biomarker, pharmacology and pathogenesis. They should withhold three of the Bradford Hill guidelines i.e. consistency, dose-responsiveness in the therapeutic range, and biological plausibility. It is found that there is no single marker of value, but that a combination of markers is best. The search of biomarkers has been impressive thorough and about 171 different tests in 56 studies found usefulness about psychoactive drugs in general.

Another type of biomarkers is about effect of drug on biomarker level. If a drug is adsorbed by charcoal and is excreted into the gut via the liver or secreted via enterocytes, activated charcoal will prevent its reabsorption. This property of activated charcoal has been put to good use in the treatment of self-poisoning. For example, in a large, randomized, placebo-controlled trial in cardiac glycoside poisoning in Sri Lanka, due to ingestion of yellow oleander seeds taken with suicidal intent, multiple-dose activated charcoal reduced mortality from 8% to 2.5%, a striking

effect. Stass et al. have used this action of activated charcoal for a different purpose and as an exogenous pharmacological biomarker of the extent to which enterohepatic or enteroenteric recycling contributes to the systemic availability of moxifloxacin [14]. Oral charcoal increased the clearance of a single intravenous dose of moxifloxacin by about 24%.

Therefore following points should be taken in account:

1. A clear, consistent response across studies (from different research groups) and drugs from the same class
2. A clear response of the biomarker to therapeutic doses
3. A dose (concentration)–response relationship
4. A plausible relationship between the biomarker, the pharmacology of the drug class and the pathogenesis of the therapeutic area.

Several studies observed that the use of biomarkers provides definite clue for the occurrence of ailment, a study of adherence of middle-aged patients to statins, given the premise that age and pre-existing cardiovascular disease are the best markers of the risk of stroke and heart attack [15-18]. Also it has been found that the potential use of the prevalence of khat chewers in populations in which the habit is common as a marker of the effectiveness of a heart attack prevention programme, since chewing khat is associated with a greatly increased risk of myocardial infarction [19]; the use, in a Chinese population taking warfarin, of the INR as a marker of the risks of major bleeding or thromboembolism, the potential use of measurement of the N-terminal propeptide of type III procollagen as a marker for the haemodynamic effects of spironolactone [20].

CONCLUSIONS

Biomarker (surrogate endpoints) is a biological indicator and can predict pathobiological state or conditions of living being. It is generally used for a substance whose presence in living system indicates the existence of certain conditions in living organisms. Biomarkers can be measured and evaluated to examine normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. It is well known that using biomarkers provides clear potential benefits for correct early prediction, diagnosis and intervention. It can help to disseminate information about fatality much earlier, more quickly, and more cheaply. However, the chain of events in a disease process linking pathogenesis to outcome is fragile and the better understanding the nature of the path a disease takes and the pharmacology of a drug that affects it. Also, better new biomarkers developed will provide in the assessment of diagnosing, staging, and monitoring disease and its response to therapy.

REFERENCES

1. Mandal, Ananya. Biomarker - What is a Biomarker?, News-Medical, An AZo Network Site, http://www.news-medical.net/health/Biomarker-What-is-a-Biomarker.aspx
2. Aronson JK. biomarkers and surrogate end-points. Br J Clin Pharmacol. 2005, 59(5): 491–494.
3. Schulte PA. A conceptual and historical framework for molecular epidemiology. In: Molecular epidemiology: principles and practices (Schulte PA, Perera FP, eds), San Diego: Academic Press, 1993, pp 3-44.
4. Merikangas K. Genetic epidemiology: bringing genetics to the population–the NAPE Lecture 2001. *Acta Psychiatr Scand* 105:3–13, 2002.
5. Muller U, Graeber MB. Neurogenetic diseases: molecular diagnosis and therapeutic approaches. *J Mol Med* 74:71–84, 1996.
6. Mayeux, Richard. Biomarkers: Potential Uses and Limitations, NeuroRx_: The Journal of the American Society for Experimental NeuroTherapeutics, 2004, 1, 182–188.
7. Mosca L, Banka CL, Benjamin EL, Berra K, Bushnell C et al. Evidence-Based Guidelines for Cardiovascular Disease Prevention in Women: 2007 Update. Circulation.2007; 115: 1481-1501.
8. Khoja L, Lorigan P, Dive C, Keilholz. and, Fusi A4. Circulating tumor cells as tumor biomarkers in melanoma: detection methods and clinical relevance. Ann Oncol. 2014 June 6, 207.
9. Fischer K, Kettunen J, Wu¨ rtz P, Haller T, Havulinna AS, et al. (2014) Biomarker Profiling by Nuclear Magnetic Resonance

Spectroscopy for the Prediction of All-Cause Mortality: An Observational Study of 17,345 Persons. PLoS Med 11(2): e1001606.

10. Aronson JK. Biomarkers and surrogate endpoints in monitoring therapeutic interventions. In: Evidence-Based Medical Monitoring: From Principles to Practice, eds Glasziou P, Irwig L, Aronson JK. Oxford: Wiley-Blackwell Ltd, 2008; 48–62.
11. Chen XH, Huang S, Kerr D, Biomarkers in clinical medicine, IARC Sci Publ. 2011, 163, 303-22
12. Bernadette Biondi B and Wartofsky L. Treatment with thyroid hormone. Endocrine Reviews. 2014, 35: 433–512.
13. Pinazo-Duran MD, Moreno VZ, Medina JGJ and Pinazo RG. Evaluation of presumptive biomarkers of oxidative stress, immune response and apoptosis in primary open-angle glaucoma. Current Opinion Pharmacology. 2013, 13: 98-107.
14. Stass H1, Dalhoff A, Kubitza D, Schühly U. Pharmacokinetics, safety, and tolerability of ascending single doses of moxifloxacin, a new 8-methoxy quinolone, administered to healthy subjects. Antimicrob Agents Chemother. 1998, 42:2060-2065.
15. Avorn J et al. Persistence of use of lipid-lowering medications. A cross-sectional study. JAMA 1998, 279: 1458-1462.
16. Benner JS et al. Long-term persistence in use of statin therapy in elderly patients. JAMA 2002, 288: 455-461.
17. Jackevicius CA et al. Adherence with statin therapy in elderly patients with and without acute coronary syndromes. JAMA 2002, 288: 462-467.
18. Simons LA et al. Apparent discontinuation rates in patients prescribed lipid-lowering drugs. Med J Aust 1996 164: 208-211. Br J Clin Pharmacol. May 2005; 59(5): 574–581.
19. Al-Motarreb A, et al. Khat chewing is a risk factor for acute myocardial infarction: a case-control study. Br J Clin Pharmacol. 2005, 59: 574–581.
20. Wong RS, Cheng G, and Chan TY, Use of herbal medicines by patients receiving warfarin, Drug Safety 2003; 26: 585-588.

