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Role of Biomarkers in Cancer Research and Drug Development

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ABSTRACT

Biomarkers as characterizing agents of patient colony and quantifying factors to a specific degree to which developing drugs reach the intended targets, induce alternation of proposed pathophysiological mechanism and obtain desirable clinical results. These specific molecular signatures have been emerged rapidly in cancer research and cancer related drug development programs and have been helped vigorously in validation of novel drug targets and prediction of drug response which together lead to precise and strong treatment of cancer diseases. In this paper we have discussed emergence of biomarkers in drug development linked to cancer treatment and highlighted their significant role in the mentioned area. The purpose of this review is to redefine the biomarker evolution in drug development related to different types of cancers and a brief background about their classification, their assessment and technologies used for their identification in order to encourage scientists for strong focus on biomarkers in their research programs related to cancer treatment. Several types of biomarkers are discussed in this paper are such as biomarkers for breast, prostate, colon, ovarian, lung, cervical cancers, hepatocellular carcinoma, nasopharyngeal carcinoma and myeloid leukaemia.

Keywords: Biomarkers, Cancer Research, Drug Development, Target Validation, Biomarker Classification

I. INTRODUCTION

Cancer as the second cause of death among high risk human diseases developed due to alternation of genome, hence tumour growth dynamics and diagnosis at molecular level are essential elements for supporting therapeutics .Although classification of human tumours is based on the site of origin and their morphological and anatomical assessment relied on tumor node metastasis (TNM) with the help of histopathological methods , monitoring progression of diseases is supplemented by application of prognostic biomarkers which are able to predict the clinical results of a therapy .So the emergence of biomarkers in drug development is prominent from this point that they play an important role in characterization of cancers and quantifying of new drugs to an specific extent in order to reach the proposed targets, change intended pathophysiological systems of the body and obtain desirable clinical outcomes .Biomarkers are diagnostic which are considerately measured and assessed as an indicator of normal biological and pathophysiological conditions or pharmacological responds to a therapeutic mediation .[1,2]. They also help in determination of surrogate endpoint and facilitate rational basis for lead compound selection .Generally biomarkers based on their clinical application classified in the following groups: Type 0: These group of biomarkers supposedly measure innate history of a disease and correspond over time with known clinical indicators. Type I: These types of biomarkers indicate the mediation effect of, for example a remedial drug and Type II: These biomarkers are seen to be both surrogate endpoint markers and clinical endpoints. Another classification of biomarkers relied on quantitative indicators of common biological or pathogenic conditions, or drug responses. These

biomarkers are useful for prediction and treatment of diseases and furnished with one or more of the following assets : 1: Biomarkers that are particularly linked with disorders in a population 2: those are inherited 3: Independence and presence state , regardless of the presence of clinical phenotype of the disorder .4: Co-dissociation with illness within families and, 5: presence in family's relatives with illness at a higher rate than in the common population .Classification of above discussed biomarkers which are in association with diseases are as follow: 1: Protein biomarkers: Proteomic assessment provides a direct measurement of the alternation in levels of protein in biological samples 2: NA-base molecular biomarkers : Utilization of mRNA – expression profiling gives highly proper and reproducible estimation of mRNA in patients 3:small molecule as biomarker : Metabolomics can provide understanding intracellular concentrations of small molecules such as proteins , amino acid, organic acids , sugar and other small molecules which are associated with diseases phenotypes 5: Single nucleotide polymorphism (SNP): As single base pair loci in genome that show variation among individuals in one or numerous populations , these biomarkers are used to determine common diseases such as cancer , heart diseases and diabetes which are susceptible in contribution to the traits that make them unique individuals. In clinical attempts biomarkers are classified in the following way: Preventive biomarkers: These types of biomarkers diagnose individuals at increased risk for pathology development. Diagnostic biomarkers: Their role is identification of the disease presence at the earliest stage before clinical symptoms. Prognostic biomarker: Their role is stratification of risk of diseases progression in patients experiencing actual therapy .Predictive biomarkers: Their role is identification of patients who are mostly expected to respond to particular therapy. Therapeutic biomarkers: Their role is measurement of response in patients experiencing therapy .Special biomarkers: Their role is identification of patients at the risk of development of adverse reactions to specific drug and therapy . We already discussed different classification of biomarkers, the current biomarkers are widely used are mRNA, proteins,SNP, expression profiling and small molecules . The most important and basic issues supported their emergence in biomarker discovery filed are cost, time and appropriate and suitable technologies .Identification of biomarkers involves combination of several technologies which together help in investigation of disease stages at all levels. The stages in biomarker identification are as follow: analysis of samples, target discovery, target validation, preclinical development, clinical development and approval. Assessment of biomarkers are carried out by following assays: single nucleotide polymorphism, bioimagaing, immunoassays , mass spectrometry and quantitative polymerase chain reaction. For biomarker discovery some genomic technologies are applicable which are such as SNP genotyping by DNA microarray which is used for identification of disease gene, microsatellite instability through linkage analysis and positional cloning which are used for mapping disease positions, expression arrays which is used for identification of deregulated genes and signalling routs , comparative genomic hybridization arrays and exon arrays which are used for loss of heterozygosity and amplification of gene . Moreover proteomic and metabolic technologies are used in biomarker discovery for example ,proteomic platforms are such as HPLC, ICAT-MS,LC-MS, MALDI-TOF, MALDI-QTOF and Liquid chromatography which participate in identification of hydrophilic and hydrophobic proteins using blood, urine, saliva , CSF and affected tissues as their samples . Gel electrophoresis, DI GE-MS, 2DE and tissue microarrays participate in detection differences between proteins of two different samples, analysis of protein biomarkers, identification of targets and biomarker validation. All these techniques use affected tissue as their analysing samples. Metabolic platforms are used in biomarker discovery are NMR for identification of small molecules such as amino acids, organic acids, sugars and so on and MS used in identification and characterization of small molecules . The metabolic technologies used saliva,

urine, blood, CSF, serum and cells as their analysing samples. [2-4] Although these techniques are helpful in identification of biomarkers but new technologies have emerged in last decay which are very helpful in identification of biomarkers and saving the time and cost for example , bioinformatics tools for SNP detection [5] and emergence of new animal model of zebra fish and it's biomarkers for screening the developing drugs .[6].

II. METHODS AND MATERIAL

Role of biomarkers in cancer research and drug development:

Biomarkers play significant role in drug development and especially in cancer research. In this section we focus on previous and recent discoveries related to cancer specific biomarkers to demonstrate their broad area of use in cancer research .Cancer specific biomarkers are discussed here are such as biomarkers are associated in detection of prostate cancer, hepatocellular carcinoma, colon cancer, breast cancer, ovarian cancer,myeloid leukaemia ,nasopharyngeal carcinoma, lung cancer and cervical cancer.[2].

Role of alpha-methylacyl CoA racemase in prostate cancer: Alpha-methylacyl CoA racemase (AMACR) is a cancer specific biomarker which is show overexpression in prostate cancer as compared to benign prostatic tissue. Researchers explored the use of alpha-methylacyl CoA racemase as a biomarker for prostate cancer. They have used immunohistochemistry for determination of AMACR protein expression. In their research, they have used an image analysis system on two localized prostate cancers groups including radical prostatectomy treated group (204 men) and 188 men followed waiting . In this research, the end points for the groups were the time to prostate-specific antigen (PSA) failure and time to prostate cancer death in the attentive expectant group. For best differentiation prostate cancer outcome in each of the groups, a regression tree method used to determine optimal AMACR protein expression cut-points separately. For examination of the effect of the AMACR cut-point on prostate cancer outcome, and adjusting for clinical variables, Cox proportional hazard models were used. Their results shown that lower expression of AMACR tissue was in association with worse prostate cancer results. Their research was the first one which showed that significant association of AMACR expression with prostate cancer and defined it as biomarker of aggressive prostate cancer.[7]

Role of alfa-fetoprotein (AFP) biomarker in detection of Hepatocellular carcinoma (HCC): HCC as a large cause of cancer death is usually diagnosed after developing clinical retrogression at which measurement of time survival is carried out in months. Control of high risk patients for HCC is usually carried out using the serum marker alfa-fetoprotein (AFP) along with ultrasonography. Initial elevation of AFP levels is seen in the early stages of HCC and then decline or even normalizes before increasing again as disease progression follows. [8, 9].

Role of adenomatous polyposis coli (APC) in colon cancer :Mutation in the adenomatous polyposis coli (APC) sometimes result in sporadic colorectal cancers.Colorectal cancers are raised through a regular course of histological alternations named as 'adenoma-carcinoma' sequence , each associated by a genetic change in a particular oncogene or tumor suppressor gene . Failure in APC function activates this chain of molecular and histological alternations. Generally, an intestinal cell requires to come around with two essential conditions to develop into a cancer. These two requirements are initial colon cancer expansion, and genetic instability which are fulfilled by inactivation of APC.[10].

Role of biomarkers in breast cancer research: Recently several biomarkers associated with breast cancer are identified, in this part we explained some of them which are both established and emerging .*Estrogen receptor (ER)* : It is the most significant biomarker in breast cancer, because it provides the indication for endocrine therapy sensitivity . ER-positive tumors which contain approximately 80% of breast cancer use the steroid hormone estradiol as their critical growth cause, therefore ER is the direct target of endocrine treatments. The studies have been confirmed that ER-negative breast cancer patients have no profit from five year adjuvant therapy with tamoxifen, but some profit may be obtained in the exceptional group of ER-negative and progesterone receptor (PgR)-expressing breast tumors. Such therapy decreases the annual breast cancer death by 31% in ER-positive cases.[11].Another biomarkers associated with breast cancer is *progesterone receptor (PgR)* .Progesterone receptor expression highly

dependent on the ER presence. Tumors exhibit PgR expression but not the Er are rare and exhibit <1% of all breast cancer patients. [12]. Because of this reason, tumors expressing PgR without ER expression should be retested for their ER status for elimination of false ER negativity. In some uncommon cases when PgR – expression without ER expression present, Sometimes tamoxifen is described , but endocrine treatment is still highly recommended.[13].*HER2* is another breast cancer related biomarker. HER2 is overexpressed in about 15% of all primary breast cancer .The best treatment for such cases is significant benefit from anti-HER2 therapies. Assessment of HER2 status in every detected case of breast cancer should be done. [14,15].Some other biomarkers related to breast cancer are Breast cancer anti –estrogene 1 resistance (BCAR 1) , Glutathion S-transferase _1 (GSTP_1), Urokinase type plasminogene activator (uPA) and Tyrosine kinase receptor (HER-2). Some emerging biomarkers in cancer research have been developed such as *ki67* which is first investigated by scientists [16]. In this investigation , scientist used a mouse monoclonal antibody in contrast to a nuclear antigen which is derived from a Hodgkin's lymphoma cell line.ki67 is a proliferation biomarker and its prominent characteristic is universal expression among proliferating cells and its absence in quiescent cells [17].*Cyclin D1* is another emerging biomarker for breast cancer .Its characteristic is its overexpression at the mRNA and protein levels in about 50% of breast cancer patients containing 15% in which occurrence of a gene amplification exist, [18-20].*Cyclin E* is another emerging biomarker for breast cancer .Its act is similar to cyclin D1 and its gene amplification has been identifried in several breast cancer cell lines[21]. It is strongly evidenced that Cyclin E play an important role in tumorigenesis [22,23]. Another emerging biomarker related to breast cancer is *ERβ*.[24,25]

Role of biomarkers in ovarian cancer: *Cancer antigen 125 (CA 125*) and *cancer antigen 15.3 (CA 15.3*) are ovarian cancer biomarkers. Cancer antigen 125 is a protein which is present on the surface od many ovarian cancer cells .This protein can be present in other type of cancer as well as healthy tissue in small amounts. Due to this presence Ca-125 is used as a biomarker for identification of ovarian cancer. In a research study, determination of CA 125 and CA 15.3 antigens is carried out by enzyme immunoassay in 78 cases with ovarian cancer for a total of 540 determinations .Investigation of the antigens in sera from 100 women with other gynaecological diseases is done. Evaluation of CA 15.3 reference values in 91 normal healthy women is carried out . The results showed that the sensitivity of CA15.3 at diagnosis and its relapse detection were lower than that of CA 125. Aspecific mesothelial cell reaction does not increase Ca 15.3 which showed that more specificity of CA 15.3 than CA 125. Combination use of both biomarkers are helpful in early detection of relapse which demonstrated their significant role as biomarkers for ovarian cancer.[26,27].

Role biomarker in Myeloid leukaemia ,: A prognostic marker known as of BCR-ABL play an important role in Chronic myeloid leukemia (CML). A chimeric oncogene Bcr-Abl is formed due to fusion between the Abelson (Abl) tyrosine kinase gene at chromosome 9 and the break point cluster (Bcr) gene at chromosome 22, which after activation result in development of Chronic myeloid leukemia . this activated chimeric oncogene Bcr-Abl is employed as biomarker in detection of CML.[28].

Nasopharyngeal carcinoma(NPC) is detected at early stage using combination of ENO1 and CYPA by quantitative proteomic analysis. In this study , scientists combined 2D-DIGE with MALDI-TOF-MS analysis for identification novel biomarkers for early detection of NPC. In this approach they performed the experiment for identification of expressed proteins in the cancer development and progression of NPC via LCM-purified normal nasopharyngeal epithelial tissues and various stages of NPC biopsies. They identified 26 differentially expressed proteins , of two proteins show direct expression change in the carcinogenesis process they named as ENO1 and CYPA,and their validation carried out by western blot analysis. They identifies as biomarkers for detection of early stage of nasopharyngeal carcinoma (NPC). [29]

Other cancer specific biomarkers are epidermal growth factor receptor (EGFR) which is biomarker for lung cancer identification when mutated. [30].Human papilloma virus DNA (HPV) for invasive cervical cancer, in this case induction of deregulation of miRNA expression is carried out by HPV and this deregulation is through E6 and E7 proteins targeting miRNA transcription factors including p53. [31].Detection of primary tumours of bladders, found in urine sample is

done using microsatellite alternations, Mutl.homologue 1(MLH 1). MLH-2 and MLH-6 are biomarkers of hereditary nonpolyposis cancer and Epstein –Bar virus DNA (EBV) serves as biomarker for detection of nasopharyngeal carcinoma. [2].Although number of established and emerging biomarkers specific to cancer diseases are not limited to above mentioned biomarkers but these are most important and well-studied examples to support the significant role of biomarkers in cancer research and drug development. Additionally biomarkers are helpful in assessment of harmful effects of new drugs; they also are used for determination of potential toxicity of drugs. This broad area of use of biomarkers in cancer research and drug development can be integrated with new technologies and bioinformatics and biostatics methodologies which result in efficient contribution to better cancer control via biomarker and drug discoveries.[2,3]

III. CONCLUSION

The fact that the cancer is a flexible disease and consists of various types with different biological behaviour, molecular and risk profiles. Flexibility nature of the cancer requires different factors such as prognostic and predictive factors for individualized therapy of cancers. Biomarkers are the most important prognostic and predictive factors in cancer research and drug development in order to achieve individualization of cancer therapy. Biomarker discovery furnish a broad area of use in cancer research and drug development such as early diagnosis of cancers, progression monitoring of cancer, anti-cancer drug responses validation, providing low risk profiles from extra side effects of over-treatment and establishing endpoints. Although biomarker discovery have been currently improved but due to sensitivity of this research area , special attention requires to be paid for designing and conduction of related clinical trials which support validation of emerging biomarkers for cancer diseases . Careful and appropriate assessment for designing, validation methods and collection of appropriate samples such as blood, quality tissues are actual requirement to address the clinical question for which the biomarker have been emerged and selected. Despite, advancement in biomarker discovery and suitable strategy support identification of biomarkers at all levels such as RNA, DNA, proteins and small molecules but compiling of the brad data resulting from this attempt will require comprehensive bioinformatics and biostatics methods. Integration of all these requirements will be helpful in providing important contribution to biomarker discovery. For individualized cancer therapy all aspects and essential elements should be employed not only biomarker identification will be result in individualization of therapy but also all types of drug targets such as CDKs,[32] ion channels,[33] GPCRs [34] and aquaporins [35] should be assessed and their assessment and validation should be correlated in all biological aspects to cover all points of treatment in order to reach a comprehensive specific individualized therapy.

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