Structural Biomarker Analysis for Brain and Blood Cancer using Bioinformatics Methods

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Abstract

We have identified the following biomarkers (protein and targets) for brain & blood cancer: DNA topoisomearase, Epidermal growth factor, Estrogen receptor, Adenosine deamenase, Receptor protein tyrosine kinase, Arachidonate 5-lipoxygenase and B-Raf proto-oncogenase\threonine- protein kinase. Biomarkers have considerable impact on the care of patients and are urgently needed for advancing diagnostics, prognostics and treatment of disease. This survey article highlights emerging bioinformatics methods for biomarker discovery in clinical metabolomics. This demonstrates that clinical bioinformatics has evolved into an essential element of biomarker discovery, translating new innovations and successes in profiling technologies and bioinformatics to clinical application.

Keywords: Adenosine deamenase, Arachidonate 5-lipoxygenase, Biomarker, B-Raf proto-oncogenase\threonine- protein kinase, ,DNA topoisomearase ,Epidermal growth factor, Estrogen receptor, Receptor protein tyrosine kinase

I. INTRODUCTION

A biomarker, or biological marker, generally refers to a measurable indicator of some biological state or condition. Further life forms are known to shed unique chemicals, including DNA, into the environment as evidence of their presence in a particular location. Biomarkers are often measured and evaluated to examine normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. Biomarkers are used in many scientific fields. It is a naturally occurring molecule, gene, or characteristic by which a particular physiological process, disease can be identified. The National Cancer Institute (NCI), in particular, defines biomarker as a: "A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease. . Biomarker regulatory validation under goes following steps: Proof of concept, Experimental validation, Analytical performances validation, Protocol standardization.

A. Abbreviations and Acronyms:

DNA: deoxyribonucleic acid, Fig: Figure, ALOX-5: Arachidonate 5-lipoxygenase, EGFR: epidermal growth factor receptor, ER: Estrogen receptors, RNA: ribonucleic acid, rRNA: ribosomal ribonucleic acid, RTK: Receptor tyrosine kinases, VGEF: Vascular endothelial growth factor, PGF: Polypeptide Growth Factor, FDA: Food and Drug Administration, QSAR: Quantitative Structure-activity Relationship.

II. RELATED WORK

A cancer biomarker refers to a substance or process that is indicative of the presence of cancer in the body. A biomarker may be a molecule secreted by a tumor or a specific response of the body to the presence of cancer. Genetic, epigenetic, proteomic, glycomic, and imaging biomarkers can be used for cancer diagnosis, prognosis, and epidemiology. Ideally, such biomarkers can be assayed in non-invasively collected biofluids like blood or serum.

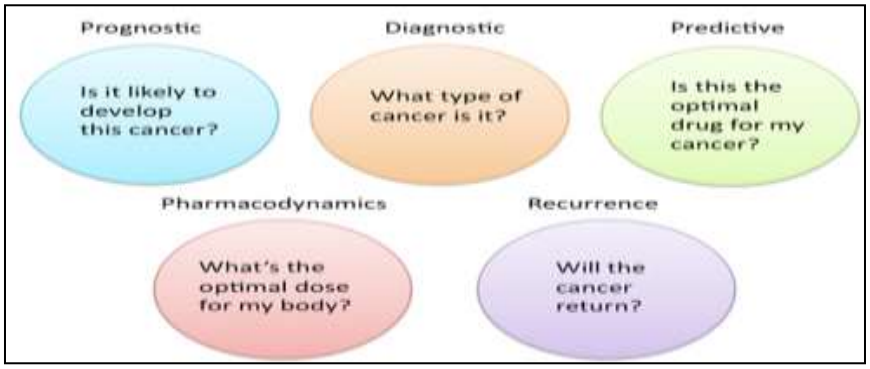

Fig. 1: Stages in cancer research and medicine

In cancer research and medicine, biomarkers are used in three primary ways:

- To help diagnose conditions, as in the case of identifying early stage cancers (Diagnostic)
- To forecast how aggressive a condition is, as in the case of determining a patient's ability to fare in the absence of treatment (Prognostic)
- To predict how well a patient will respond to treatment (Predictive)

III. FRAME WORK

The following are the biomarkers identified for brain & blood cancer:

A. DNA topoisomearase:

DNA topoisomerases are ubiquitous enzymes found in all cell types from viruses to man. These enzymes act to regulate DNA supercoiling by catalyzing the winding and unwinding of DNA strands. They do this by making an incision that breaks the DNA backbone, so they can then pass the DNA strands through one another, swiveling and relaxing/coiling the DNA before resealing the breaks. DNA topoisomerases can be divided into two groups based on the number of strands that they break. Function: The reaction catalyzed by the topoisomerases leads to the conversion of one topological isomer of dna to another.

B. Epidermal Growth Factor Receptor:

The epidermal growth factor receptor (EGFR) is the cell-surface receptor for members of the epidermal growth factor family (EGF family) of extracellular protein ligands. Function: The nucleus is involved in transcriptional regulation and activates its transcription. Involved in transcription of rRNA genes by RNA. Enhances protein synthesis and cell growth. Role in cancer: Mutations that lead to EGFR over expression (known as up regulation) or over activity have been associated with a number of cancers, including squamous-cell carcinoma of the lung (80% of cases), anal cancers, glioblastoma (50%) and epithelian tumors of the head and neck (80-100%). These somatic mutations involving EGFR lead to its constant activation, which produces uncontrolled cell division Mutations, amplifications or misregulations of EGFR or family members are implicated in about 30% of all epithelial cancers.

C. Estrogen Receptor:

Estrogen receptors (ERs) are a group of proteins found inside and on cells. They are receptors that are activated by the hormone estrogen (17β-estradiol). Two classes of ER exist: nuclear estrogen receptors (ERα and ERβ), which are members of the nuclear receptor family of intracellular receptors, and membrane estrogen receptors (mERs), which are mostly G protein-coupled receptors. This article refers to the former (ER).Function: Involved in regulation of eukaryotic gene expression and affect cellular proliferation and differentiation in target tissues. Role of Estrogen receptor in Cancer: Estrogen receptors are over-expressed in around 70% of breast cancer cases, referred to as "ER-positive", and can be demonstrated in such tissues using immunohistochemistry. Two hypotheses have been proposed to explain why this causes tumor genesis, and the available evidence suggests that both mechanisms contribute: First, binding of estrogen to the ER stimulates proliferation of mammary cells, with the resulting increase in cell division and DNA replication, leading to mutations. Second, estrogen metabolism produces genotoxic waste.

D. Adenosine Deaminase:

Adenosine Deaminase (also known as adenosine aminohydrolase, or ADA) is an enzyme (EC 3.5.4.4) involved in purine metabolism. It is needed for the breakdown of adenosine from food and for the turnover of nucleic acids in tissues. Function: Catalyzes the hydrolic deamination of adenosine and 2-deoxyadenosine.Plays an important role in purine metabolism and in adenosine homeostasis. Contributes indirectly to cellular signaling events. Use of adenosine deaminase for cancer therapy: The invention provides new methods of treating and inhibiting tumors, and especially malignant solid tumors, by administering adenosine deaminase in order to reduce tissue levels of adenosine and deoxyadenosine.

E. Receptor tyrosine kinases (RTKs):

They are the high-affinity cell surface receptors for many polypeptide growth factors, cytokines, and hormones. Of the 90 unique tyrosine kinase genes identified in the human genome, 59 encode receptor tyrosine kinase proteins. Receptor tyrosine kinases have been shown not only to be key regulators of normal cellular processes but also to have a critical role in the development and progression of many types of cancer. Receptor tyrosine kinases are part of the larger family of protein tyrosine kinases, encompassing the receptor tyrosine kinase proteins which contain a transmembrane domain, as well as the non-receptor tyrosine kinases which do not possess transmembrane domains. Function: Receptor for VEGF and PGF, and has a tyrosine-protein kinase activity. The VEGF-kinase ligand/Receptor signaling system plays a key role in vascular development and regulation of vascular permeability

F. Arachidonate 5-lipoxygenase:

Arachidonate 5-lipoxygenase, also known as ALOX5, 5-lipoxygenase, 5-LOX, or 5-LO, is a non-heme iron-containing enzyme (EC 1.13.11.34) that in humans is encoded by the ALOX5 gene. Arachidonate 5-lipoxygenase is a member of the lipoxygenase

family of enzymes. It transforms EFA substrates into leukotrienes as well as a wide range of other biologically active products. ALOX5 is a current target for pharmaceutical intervention in a number of diseases Function: Catalyzes the first step in leukotriene biosynthesis and thereby plays a role in inflammatory processes.

G. B-Raf Proto-Oncogene, Serine/Threonine Kinase:

BRAF is a human gene that encodes a protein called B-Raf. The gene is also referred to as proto-oncogene B-Raf and v-Raf murine sarcoma viral oncogene homolog B, while the protein is more formally known as serine/threonine-protein kinase B-Raf. Drugs that treat cancers driven by BRAF mutations have been developed. Two of these drugs, vemurafenib and dabrafenib are approved by FDA for treatment of late-stage melanoma. Vemurafenib was the first drug to come out of fragment-based drug discovery Function: Involved in transduction of mitogenic signals from cell membrane to nucleus. Plays role in postsynaptic responses of hippocmpal neuron.

IV. EXPERIMENTAL RESULTS

In this project we use the softwares Hyperchem, Swiss pdb viewer and gold docking to analyze the experimental results. By using Hyperchem software functions like model build, Visualization of 3D STRUCTURE, Calculation of parameters like Bond Distances, Bond Angles, Torsional Angles, Energy minimization, Gradient are done. Convergence of a molecule can be known. Calculation of QSAR PROPERTIES, Molecular Dynamics, total Energy are also done.

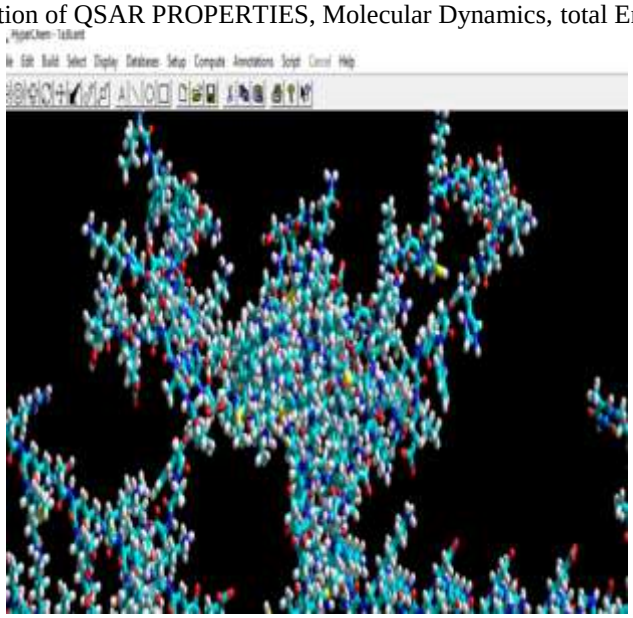

Fig. 2: Ball and sticks rendering view of DNA topoisomerase

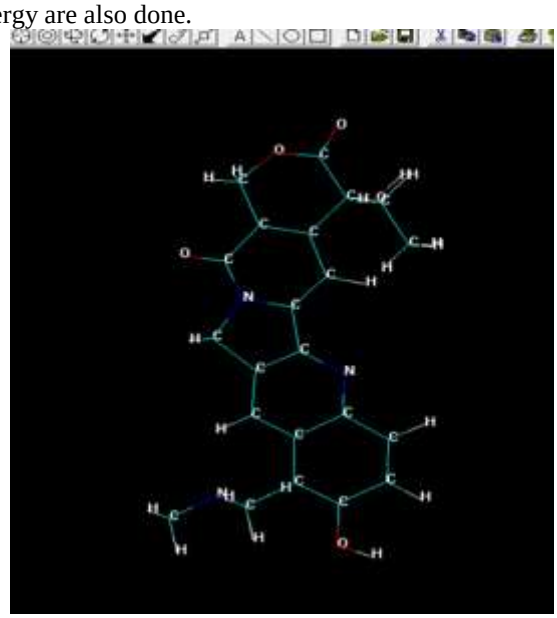

Fig. 3: Topotecan

Swiss-PdbViewer is an application that provides a user friendly interface allowing to analyze several proteins at the same time. The proteins can be superimposed in order to deduce structural alignments and compare their active sites or any other relevant parts. Amino acid mutations, H-bonds, angles and distances between atoms are easy to obtain. The protein sequence can also be known. We can get the FASTA sequence by using NCBI web tool.

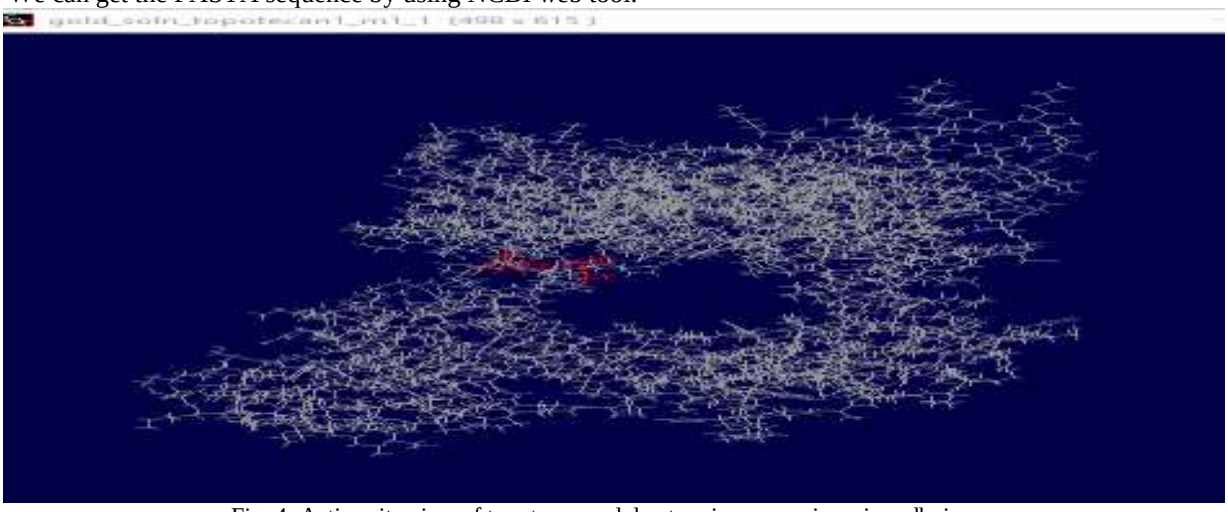

Fig. 4: Active site view of topotecan and dna topoisomerase in swiss pdbviewer

GOLD is highly configurable allowing you to take full advantage of your knowledge of a protein-ligand system in order to maximize docking performance. GOLD enables complete user control over speed versus accuracy settings, from efficient virtual screening of large compound libraries, to highly accurate exhaustive sampling for lead optimization. With a wide range of available scoring functions and customizable docking protocols, GOLD provides consistently high performance across a diverse range of receptor types.

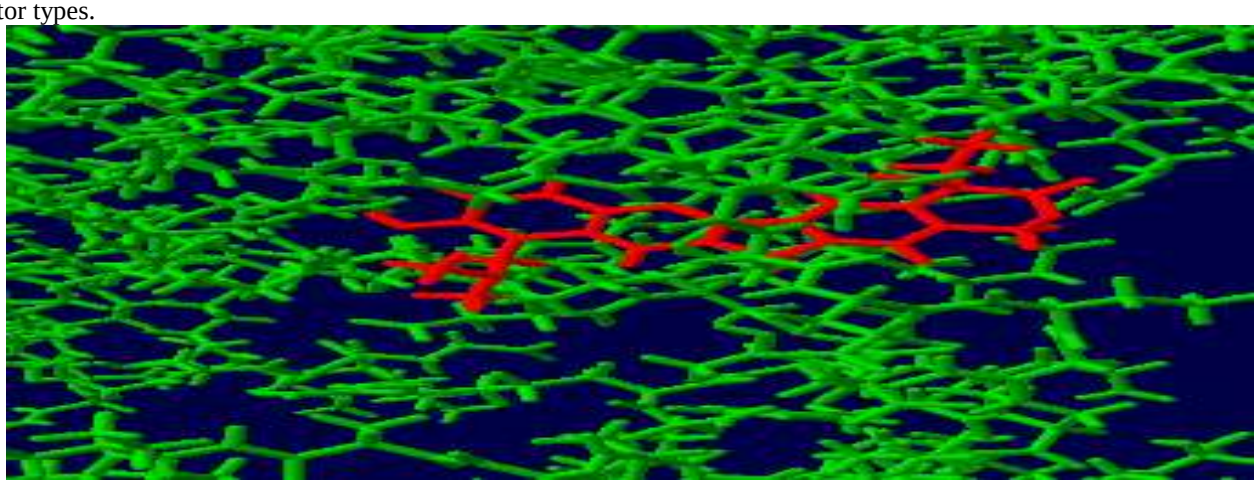

Fig. 5: Docking of Topotecan and DNA Topoisomerase

V. CONCLUSION

By analyzing the information provided in experimental results a drug can be introduced in the medicinal field which helps in treatment of the above mentioned cancer biomarkers. As we are providing all the information like fasta sequence, protein sequence, inhibitor, drug, class, pdbs,UniprotId.,structure of each target regarding the biomarkers it makes easy for the researchers to treat the cancers even in late stage. Use of Biomarkers in cancer medicine include Risk assessment, Diagnosis, Prognosis and treatment predictions, Pharmacodynamics and pharmacokinetics, Monitoring treatment response and, Recurrence. Uses of biomarkers in cancer research include Developing drug targets and Surrogate endpoints.

REFERENCES

[1] Nucleic Acids Res. 2015 Oct 12. pii: gkv1037. The IUPHAR/BPS Guide to PHARMACOLOGY in 2016: towards curated quantitative interactions between 1300 protein targets and 6000 ligands. (Ligand id: 6823).
[2] New advances in lung cancer chemotherapy: topotecan and the role of topoisomerase I inhibitors. Oncology. 2001;61 Suppl 1:14-24.
[3] Trusted, scientifically sound profiles of drug programs, clinical trials, safety reports, and company deals, written by scientists. Springer. 2015. Adis Insight (drug id 800008909).
[4] Gefitinib ('Iressa', ZD1839) and new epidermal growth factor receptor inhibitors. Br J Cancer. 2004 Feb 9;90(3):566-72.
[5] Regulation of the estrogen receptor in MCF-7 cells by estradiol. Mol Endocrinol. 1988 Dec;2(12):1157-62.
[6] ClinicalTrials.gov (NCT00190697) A Study of LY353381 (Arzoxifene) for Patients Who Benefitted From This Drug in Other Oncology Trials and Wished to Continue Treatment. U.S. National Institutes of Health.