# Cancer Bio-Informatics
# New Future of Cancer Therapy

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**Abstract**— we all are very familiar with the name "cancer" which claims nearly 7 million lives each year worldwide. To fight against cancer different type of treatment approaches are taken and as time passes sophisticated research proposals are made. Bioinformatics is also not an exception. DNA sequencing, microarray expression profiling and genomic sequence analysis are different research fields under bioinformatics. Currently our adopted medical treatments are based on chemotherapy that are not target specific and maximizes the side effects. This article reviews and discusses recent advances in the treatment of cancer with the help of bioInformatics as many challenges yet to overcome in reduced cost and time. Traditional chemotherapy/radiation therapies are costly. It is better to have molecularly targeted therapies like ligand targeted therapy which are more targets limited, produces less toxicity and can overcome many drug resistance challenges. It is a challenge to develop accurate tools for delivering the right treatment to the right patient based on biological characterization of each patient's tumor.

**Index Terms**— Cell division; Ligand; mRNA Microarray; Vaccine; MoAbs; Gene; Antiogenesis; Epigenetic; Apoptosis; Mutation.

## 1 INTRODUCTION

TILL date, cancer remains one of the most life-threatening diseases. All current treatments were not effective for all cancers as therapy needed to reach every organ of the body. First description of cancer was found in an Egyptian papyrus around 1600 BC. It was not considered to be a curable disease until the nineteenth century, when surgery was an option by anaesthesia. Statistical analysis shows that in 2050, these numbers will rise to an expected 27 million new cases and 18 million cancer deaths (out of approx. population of 10 billion) if we cant improve our cancer treatment. Current efforts to cure cancer are focusing on drugs, bio molecules and immune mediated therapies. We are still unable to improve the mortality rate or to prolong the survival time for metastatic cancer what we expected. We have identified the diagnostics and pathways of different tumour entities. This knowledge is analysed to generate tumour specific targeted therapies.[1]

Targeted therapy provides us a wide variety of direct and in-direct targeted approaches. Direct approaches target tumour antigens to alter their signaling strategy either by monoclonal antibodies like MoAbs2 or by small molecule drugs or ligands that interacts with target proteins. Indirect approaches rely on tumour antigens on the cell surface acts as target devices for ligands that contain different kind of effector molecules. In addition to active targeting, tumors can also be targeted by macromolecules but that are passive.

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## 2 LIFE OF CANCER CELLS

### 2.1 Cancer Genetics

Detailed First, Study demonstrates that only a few of 35,000 genes in human genome have been connected with cancer. Alteration in same gene can cause different kind of cancer. These cancer causing genes are classified into proto-oncogenes, tumor suppressor, DNA repair genes. About 30 tumor suppressor & 100 dominant oncogenes have been identified so far, and the reason of this tardy progress is due to the existence of functional redundancy in human genome that makes the task of identifying cancer genes a difficult one. In humans, 287 genes out of 30,000 (with 80% redundancy) are known to be disease genes. Genetic modification hampers the encryption of cellular signalling specially protein kinases, can results in cancers. Drugs targeting mutant kinases are effective in cancer patients. The sensitivity of such drugs is linked to the genetic structure of individual tumors. Thus, mutational profiles of tumor DNA help in prioritizing anti-cancer therapy and leading patient management. Many types of gene alterations can occur in cancers & four main types include:

- point mutations or Single nucleotide variants (SNVs) .
- Frame shift mutation or framing error.
- Gene copy number changes.
- A Structural variants (SVs) or large structural glitches of genetic material including translocations or inversions.

Frequently, cancer-causing mutations cluster in “hotspots”. Tumors from different patients harbor the same repeated mutation. Some hotspot SNVs may occur often, while others are rare. For example, the BRAF V600E mutation occurs in 40% of all melanomas where the BRAF L597S mutation occurs in <1% of all melanomas [1].

### 2.2 Relation of Cancer with Cell Cycle

Mutations happening (inherited or by environmental factors such as UV light, X-rays, chemicals, tobacco products, viruses &

bacteria) in proto-oncogenes and tumor suppressor genes induce the cells to defy tight controls exerted in the cell division cycle. A glaring abnormality of the checkpoint in G1 phase has been observed. Retinoblastoma (Rb) is a tumor suppressor protein which regulates the restriction point (R) through G1 into S phase by influencing the activity of E2F family in coordinating transcription of genes involved in cell cycle progression. Phosphorylation of Rb protein by Cdks (a category of nuclear proteins) prevents the interaction with E2F so that the cell can enter S phase. In tumor cells, the Rb protein control becomes abnormal. In certain tumors, the Rb gene is mutated, preventing the binding of Rb with E2F. Deregulation of Rb/E2F pathway is the characteristic of tumor cells caused by abnormal Rb control [1,4].

### 2.3 Existing Treatments

Drugs prescribed for cancer are cytotoxic in nature. Traditional radiation and chemotherapeutic treatments have a limitation over discriminating normal & abnormal cells, hence are unable to target abnormalities associated with malignant tumor cells. These therapies, directly or indirectly, act on the cells cycle causing disturbance of the cyclic events, which are otherwise precisely controlled. Some cancers, particularly leukemia, are treated with very high doses of chemotherapy drugs and radiation to kill all the cancer cells. The side effect of this harsh treatment is destruction of the bone marrow that contains stem cells. Stem cells are immature essential cells develop into blood cells. After treatment, the patient's bone marrow must be restored. It can be done either from bone marrow removed from the patient or from a compatible donor. Chemotherapy drugs also kill certain adult cells that divide more rapidly, like cells of gastrointestinal tract, bone marrow cells, and hair follicles. The side effects of chemotherapy include gastrointestinal cell damage, low white blood cell count, hair loss etc [7]. Each year around a half-million people suffers from head and neck cancer and they undergo chemotherapy but 40 percent of them suffer major damage to their salivary glands, resulting in dry-mouth syndrome.

### 2.4 Risk of Cancer

Risk factors can include age, race, sex, genetic factors, diet, tattoos, processed meat and exposure to chemicals/carcinogens, radiation and tobacco. Genetics play a large role for many cancers like breast cancer and colon cancer. Few viruses are known to promote human cancer including DNA viruses like papillomavirus, Epstein Barr virus and human T-cell leukemia virus, KSHV and retroviruses, a type of RNA virus (HIV)). The retroviruses are able to promote cancer with the presence of oncogenes in these viruses [1].

## 3 BIOINFORMATICS IN CANCER RESEARCH

### 3.1 Why Bioinformatics

Since its commencement in the 1980s, bio-informatics has been rapidly growing, maintaining a pace with the expansion of genome sequence data. The area of cancer research is not an exception [16, 19].

### 3.2 Drug Design with Protein Structure Analysis

The molecules whose shape produces interest on structural biologists are proteins as protein molecules do much of the work in the body. The shape or structure of a protein offers hints on the part it plays in the body. It also holds the key to develop new medicines, materials, or diagnostic procedures. Proteins are made of amino acids hooked end-to-end like beads on a necklace. Many scientists believe that if deciphering the structures of proteins from their sequences becomes possible then we could better understand protein functions. Then we could use that knowledge to improve the treatment of diseases[5, 8]

Research activity at Ohio State University's comprehensive cancer center has determined the 3D structure of the protein produced by the p16 tumor-suppressor gene on the computer. When the p16 protein is missing or inactive because of mutations in the p16 gene, cancer can occur [5,8,16].

### 3.3 Cancer classification with Gene Expression Study

Traditional cancer classification methods (morphological & clinical based) are poor and are suffering from limitations in their diagnostic ability. Therefore, accurate prediction of different tumors has become important to offer better treatment & toxicity minimization on patients. Also, the existing tumor classes have been found and they are heterogeneous and consists molecularly distinct diseases that follow different clinical treatments. To gain a better perception into the problem of cancer classification different systematic approaches are taken depending on global gene expression analysis. The expression levels of genes are known to contain the keys to study fundamental problems which are related to prevention , cure of diseases with biological evolution and drug discovery [17]. Microarrays and SAGE are two recent technologies for measuring the thousands of genome-wide expression values in parallel. The first one, which consists of c-DNA microarrays and high-density oligonucleotide arrays, measures the relative levels of mRNA surplus between different samples, while the latter measures the absolute level. DNA microarray has been used by researchers to identify genes involved in metastasis. Researchers investigated the colonal relationship of 22 liver tumor foci from six patients through gene expression profiling by cDNA microarray containing 23,000 genes. This study aimed at identifying metastasis genes for liver cancer. They were able to identify a total of 63 genes (39 known genes and 24 expressed sequence tags) up-regulated and 27 genes (14 known genes & 13 expressed sequence tags) down-regulated in metastasis modules compared to primary tumors. Microarray based expression profiling has been used for studying metastasis in osteosarcoma, colorectal tumor & brain cancer. Microarray analysis also helped in identifying potential biomarker finding of lung, oesophagal, and colorectal cancers. Both Accuracy & Biological relevancy are important in cancer classification [17,18]. SAGE technology is used to facilitate the measurement of mRNA transcripts of normal and infectious tissues in a highly accurate and quantitative manner. The SAGE technique not only measure the expression level of a gene but also calculates a "tag" which represents the transcription product of that gene.

### 3.4 Current & Future scope of Targeted Therapy

They are new forms of treatment to inhibit specific molecular targets namely altered or deregulated proteins. The main objective of targeted therapy (basically drugs) is to target particular responsible molecules for malignant tumor growth & progression with minimal side effects and more accuracy. This paper includes

present & future scope of different targeted therapies as mentioned below:

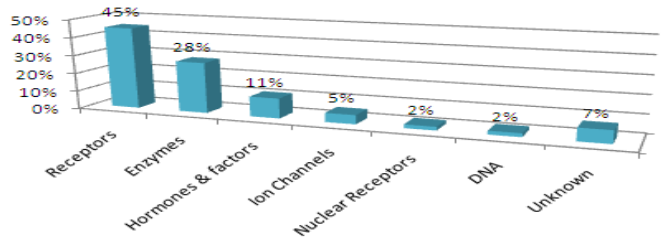


Fig.1. Drug Target Classes

**Antibody Targeted Therapy:** They are monoclonal antibodies and are used to target antigens found on the cancer cell surface like trans-membrane receptors or extracellular growth factors. They can be conjugated to radio isotopes or toxins to grant specific delivery of these cytotoxic agents to the targeted cancer cells. MoAbs (monoclonal antibody) has been generated & it is well-tolerated & effective for different cancer target therapy and it has been approved by FDA (USA). Several issues must be considered in antibody target therapy like choice of target antigen, immunogenicity of antibodies, half-life of antibody, penetration into solid tumors and ability of antibodies to recruit immune effector functions. The first antibodies studied were murine, rabbit, or rat proteins. Patients often generated antibodies to these foreign antigens, are often referred to as HAMA (human anti-mouse antibody) or HARA (human anti-rat or rabbit antibody). The host antibody reduces the efficiency of therapy either by prematurely clearing the treatment antibody or restricting the possibilities for future immunotherapy. The HAMA or HARA responses can cause adverse events such as serum sickness and anaphylaxis. [11] Solid tumors are quite heterogeneous and therefore difficult to target them completely as during targeting them, smaller recombinant MoAb structures like single thread antibodies should be able to penetrate into the tumor with higher efficiency than the parental antibody. One promising approach to solid tumors is to target the tumor microenvironment and endothelium of tumor blood vessels in particular, because several tumor endothelial markers are well characterized [11,12].

**Targeted Therapy by Small Molecules:** They are capable of penetrating the cell membrane and interacting with targets inside a cell. Small molecules are generally designed to communicate with the enzymatic activity of the target protein without causing any detrimental side-effects. Small molecule inhibitors of protein kinases are important for studying target therapy. Protein kinases mostly targeted for drug development are plasma membrane related like tyrosine kinases. The first kinase inhibitors were developed in the early 1980s by Hiroyoshi Hidaka and Naphthalene sulphonamides was developed as antagonists of the calcium-binding protein calmodulin. There are more than 30 such agents in clinical trials now and the most well-known small molecule inhibitors are glivec and gefitinib [9].

**Ligand Targeted Therapy:** Most cancer cells exhibit many common features with the normal host cells from which they are derived. Therefore, it is a challenge in anticancer chemotherapeutics. To overcome this, unique molecular targets needs to be identified that would distinguish them from normal cells. It can lead to increased toxicities in normal tissues like bone marrow, cells at gastrointestinal tract and hair follicle tissues and to avoid the side effects to normal tissues. We often provide sub-optimal doses of anti-cancer chemotherapeutics that result in eventual failure of therapy. The selective dosage level of an anticancer drug can be increased by either increasing the amount of the drug, reaches the cancer tissue or decreasing the density of drug that reaches the normal tissues. so, ligand-targeted therapy leads tumor specificity and reduced toxicity and shows promise in the development of noble therapies for cancer. The Ligand targeted therapy can pass higher doses of a drug to the tumor targeted cells and may cross over obstacles presented by cytotoxic chemotherapy. [1, 2]

**Enzyme Inhibition therapy:** Drugs like Enzyme inhibitors inhibit enzymes that signal for cancer cells to grow. Inhibition stops growing & spreading of cancer cells. The tumor is not getting smaller means its abnormal growth has been interrupted where a regular chemo can give a better chance to work. Slowing or stopping out-of-control growth rate of cells may also help people live longer, without adding other drugs. Enzyme inhibitors are called by different names based on the enzymes they block like Signal-transduction inhibitors, Tyrosine kinase inhibitors, Proteosome inhibitors and mTOR inhibitors & Growth factor inhibitors, Multi-targeted kinase or multikinase inhibitor (blocks many different enzymes). [1, 2, 5]

**Hormone Therapy:** Prime growth factor of normal cell are hormones. Although cancer cells loose some of the general responses to growth factors, but some cancer cells still require hormones to grow up. Hormone therapy for cancer attempts to starve the cancer cells. This is usually done with drugs that block the mechanism of the hormone, besides some drugs can block synthesis of the hormone. Drugs block the binding site for hormone to slow the growth of these cancers. Research proves that it is effective for prostate & breast cancer. [2, 5]

**Antiogenesis Inhibitor:** Vasculogenesis & Angiogenesis are two tightly regulated processes for vascular system development. Angiogenesis is active under specific physiological conditions in healthy adults where the vasculature can be aberrantly activated to create new blood vessels during pathological conditions such as cancer and chronic inflammation. Making of new blood vessels is a normal physical process with the growth & development of human body. Their formation rate becomes stagnant in adults but never gets stopped as new blood vessels help in healing wounds & repairing damages. But in a person with cancer, same process creates new blood vessels to provide tumor its own blood supply through which nutrients can flow to cancer cells that can be controlled or stopped by Antiogenesis Inhibitors by formation of new blood vessels for tumor cell growth. Such type of drugs work by

blocking vascular endothelial growth factor (VEGF) which is created by some tumors. The vascular endothelial growth factor proteins can attach to the VEGF receptors of blood vessel cells which causes new blood vessels to form around the tumors. If this process gets blocked it will prevent angiogenesis [10,13].

**Targeted Therapy by Pox Virus:** Research at Illinois University shows Targeted oncolytic poxviruses or vaccinia viruses have a great future for targeting, attacking and eradicating cancer cells due to their enhanced tolerability, efficacy & minimal side-effects which are limited to flu-like symptoms. The strain of pox virus has been used safely in millions of people as part of a worldwide vaccination program. The biology of pox viruses make them proper nanotech therapeutics to attack cancer with features incorporate 1) rapid and motile spread in tumors , 2) intravenous stability 3) therapeutic transgene-arming capacity & 4) antidotes are available to maximize safety. Oncolytic poxviruses can not only vaccinate the cancer patients and induce an anti-tumor immune response that additionally can cause acute tumor lysis through viral replication and cell destruction with disruption of the vasculature to the tumor. After penetrating into tumor cells, virions replicates rapidly and efficiently. Infectious virions are discharged around six hours after tumor cell infiltration, and tumor cell destruction occurs within approx. 24 hours, up to 10,000 particles released upon cell lysis and spread within tumors and to distant metastases [Jennerex Biotherapeutics]. Researches have capitalized on vaccinia viruses to create safe therapeutic viruses which can broadly infect tumors via rapid replication & spreading with the induction of long term anti-cancer immunity.

- **Apoptosis Inducing Drug Therapy:** Some targeted therapy forces cancer cells to die by changing proteins within victim cells. They are known as apoptosis-inducing drugs. Normal cancer treatments like chemo or radiation kills normal cells along with cancer infected cells. Targeted drugs are different in this context- they aim at correct victim cancer infected cell and lead it to apoptosis state. [1, 2]

## 4 CANCER VACCINES

The main objective of vaccination is to build a resistance in body against tumor Specific Antigen (TSA) and Tumor Associated Antigens (TAA). Peptide vaccines was developed based on epitope. Epitope based vaccines are designed on the basis of B and T lymphocytes. The T cell epitopes consists of peptide fragment and B cell epitopes usually made of proteins, lipids or nucleic acids or carbohydrates. Peptide vaccines against various types of cancer had been developed due to their easy production, stability and no infectious materials present in them. Cervical cancer has affected around 500,000 women in developing countries due to genital infection of human Papilloma virus. It is an DNA virus that infect basal epithelial cells. HPV vaccines are prepared from virus like particles using the recombinant DNA technology. HPV vaccine gives protection against the risk types HPV 16 and 18 and the Quadrivalent HPV vaccine also gives protection against risk genotypes like 6,11,16 & 18. Compared to all other treatment modalities like chemotherapy, radiotherapy and adaptive immunotherapy, a vaccine based immune response against the tumor may be the only way to prevent the cancer for lifetime. Prophylactic vaccines are only in research mode in animal models and far away from the application in human subjects but the development of prophylactic vaccine would definitely play a greater role in prevention of cancer. One of Several mechanisms had been delivered to instruct Antigen presenting cells like dendritic cells to enhance immune response like a) infecting dendritic cells with yeast, viral, bacterial vectors, b) by Pulsing dendritic cell with protein, peptides and capturing dendritic cells with tumor cells or tumor lysates, c) by Transfecting dendritic cells with DNA, RNA. Therapeutic cancer vaccines uses patients own immune system in pointing and removing cancer cells. Tumor Specific Antigen vaccine is difficult. Tumor Specific Antigen found in tumor cells, varies from individual to individual due to the somatic mutations on the protein sequence, thereby personalized immune response to individuals system is needed. Tumor Associated Antigens discovered in tumors with similar analysis and of different origin are weakly immunogenic because of tolerance to self antigens obtained from immune system in developmental stages, so targeting them for vaccine production is difficult. Nan-particles had been recently used as the delivery system for the Tumor Associated Antigen and adjuvant to dendritic cells so as to elicit an effective immune response against the tumor cells. Alogarithm proposals based on T cell epitope have been set up using the peptide sequence binding data with experimental binding data based on affinity using any of the methods such as Motif based systems, Hidden Markova models, ANN, Quantitative-structure based relationships, structure based approach to T cell epitope prediction and support vector machines. [14, Jennerex].

## 5 DISCOVERY OF NOBLE GENES & EPIGENETIC

The purpose of this approach is to identify transcription factor of novel genes (tumor suppressor genes & oncogenes) & regulate transcription directly or indirectly to target genes, identified with microarray related expression profiling. The P53 is a transcription factor of tumor suppressor gene that induces growth arrest/apoptosis by transcriptionally activating its target genes. The aim of Epigenetic research is to make out heritable gene regulation that is not directly caused by changes in the DNA sequence. Epigenetic regulation plays a key mechanism for cellular differentiation and cell fate decisions. Stochastic (random / non-deterministic) and environment-induced epigenetic defects are known to play a major role in cancer and ageing, and they can also contribute to mental disorders and autoimmune diseases. Epigenetic analysis of embryonic stem (ES) cells has started to uncover the basic circuitry of mammalian development and in cancer research, epigenetic opens up novel approaches for early diagnosis and treatment. Promoter prediction is an important topic in bioinformatics since the early 1990s that can be regarded as the first attempt to predict epigenetic states from the DNA sequence. A considerable amount of bioinformatics research has been committed to the prediction of epigenetic information from characteristics of the genomic sequence. Different epigenome prediction methods are like Promoter Prediction, CpG island prediction, DNA methylation prediction, Prediction of nucleosome positioning are proposed on which research is going on.

Mutations and chromosomal deletions can irreversibly destroy tumor suppressor genes and leads to cancer progression. It is now clear that due to epigenetic deactivation a good amount of silenced tumor suppressing genes are lost. Furthermore, a comparative study between the stem cells & epigenetic characteristics of cancer cells suggests that epigenetic deregulation may force cells for cancer-like behavior before they are visually identifiable as tumor cells. Thus, the important role of cancer related epigenetic defects opens up new opportunities for improved diagnosis and therapy. [15]

## 6 SPINDLE INHIBITOR

A class of drugs called spindle inhibitors (stop the synthesis of microtubules) stops cell replication early in mitosis. Experts have suggested that in order to overcome the side effects, efforts should be aimed at finding new and efficacious anticancer drugs based on identification of the cell cycle targets that interfere with the cell cycle regulatory pathway. [1, 2]

## 7 END SECTIONS

### 7.1 Challenges of Targeted Therapy

There are several obstacles in target based cancer therapy including drug resistance, high tumor interstitial fluid pressure (IFP), and cancer stem cells (CSCs) in solid tumors (CSCs are biologically distinct from other cancer cell types. Although targeted therapy drugs don't directly affect the body the same way as standard chemo drugs do, yet they still cause side effects that depend largely on what the drug targets. Some drugs target substances that are more common on cancer cells and can be found on healthy cells. So these drugs may affect healthy cells, too, causing some side effects and it happens when drugs attack more than one target. Also, drugs that act as angiogenesis inhibitors that disrupts new blood vessel formation all over the body, not just those near the cancer. This can lead to other side effects, as well like change in skin feel, rash, dry skin, itching, red sore cuticles around the nails, hand-foot syndrome, change in hair growth, and change in hair or skin color, change in and around the eyes, high blood pressure, problem with blood clotting, problem with wound healing, diarrhea, nausea & vomiting, constipation, fatigue, low blood cell count, trouble breathing etc.

## 8 CONCLUSION

The Early diagnosis of cancer increases the chance of survival so test for cancer should be conducted on regular basis. Regular genetic tests & cancer risk counselling is required if any family has strong cancer history. Genomic technology has made drug target analysis effective with the help of bio-informatics. Many new molecular targeted cancer drugs have gained approval over the last few years and have improved and extended the lives of a large number of patients. However, the discovery and development of new targeted drugs have some drawbacks like it is still frustratingly slow and have high failure rates, mainly in late stage clinical trials leading to a constant challenge. Our understanding of the genetics and molecular basis of cancer initiation and malignant advancement has improved enormously, with the help of bio-informatics. It has opened up astounding possibilities for selective therapeutic targeting to exploit addiction, dependency and vulnerabilities in cancer cells. Scientific and technological breakthroughs have enabled faster efficient drug discovery, together with more refined clinical trials. Ligand based & Virus targeted therapy have opened up new research possibilities to destroy cancer cells effectively. Researchers have suggested a novel hypothesis based on acid-mediated tumor invasion for counter-intuitive possible therapies (like increasing systemic acidity to make tumor poisoned). Cancer Vaccination has revealed a great scope of research to set up a fight against cancer with minimal side-effects. However, there is still a large amount of work that needs to be done in order to accomplish the goal of cancer assortment & discover targeted therapy for every cancer class.

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