Targeting Cancer Cell Signaling Using Precision Oncology Towards a Holistic Approach to Cancer Therapeutics

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Abstract

The mutational changes occurring in the regulatory genes responsible for the maintenance of optimal cell growth and proliferation gradually lead to cancer progression and metastasis. Furthermore, patients with the same cancer types often respond differently to different cancer therapies, indicating the need for a patient-specific treatment regimen for the disease. Precision 34 oncology is the new field of cancer research that relies on genetic profiling of individual tumors to identify targetable alterations for custom-tailored personalized treatment of the disease. It is to rely upon the genomic study of cancer cells to get a clear picture of the prognosis and pathways involved in disease progression and to look for the means to selectively target them for a cure. This article intends to briefly explain the foundations and frontiers of precision oncology in the context of technological advances being made in this direction to assess its scope and importance in the realization of a proper cure for cancer.

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Abstract:

Cancer is a devastating disease causing one in six deaths globally with a huge physical, psychological, and economic impact on the people affected by the disease. The disease is prevalent throughout the world and continues to be the second most common cause of hospital deaths after heart disease, most of which can be prevented by improving prevention and treatment strategies for the management of cancer. It requires a proper diagnosis of thedisease, the development of efficacious treatment options, and a better understanding of the socioeconomic factors that affect cancer incidence, prevalence, and related deaths worldwide [1,2]. More than 100 cancer types with subtypes have been determined based on location, cell of origin, and genetic variations that influence oncogenesis and therapeutic response. Most cancers appear in epithelial cells as carcinomas, such as lung, skin, breast, liver, colon, prostate, and pancreas cancer, whereas sarcomas arise from mesenchymal tissues, originating in, myocytes, adipocytes, fibroblasts, and osteoblasts. Tumors can also develop in hematopoietic tissues such as leukemia and lymphoma and in the nervous tissues, e.g., gliomas, and neuroblastomas. They are among the most common cancer types taking a high toll in terms of lives and property across the world [3,4]. Considering the vast number of incidences, a formal initiative to address the menace of cancer was called for, on part of the government system in parts of the world which first appeared in the United States as the National Cancer Act of 1971 signed by President Richard Nixon aimed at promoting cancer research and application of the outcomes for minimizing cancer incidences and mortality rates associated with the disease. The act was euphemistically described as the "War on Cancer", and theyear 2021 marked the 50th anniversary of signing of the act into law [5]. The National Cancer Program that was borne from this initiative resulted in a concerted effort across the length and breadth of the country to develop the infrastructures required for treatment, cure and eradication of cancer. A similar approach was adopted by most other developed and developing nations in the following years to combat cancer as the leading cause of death globally, and it has succeeded in satisfying the purpose to a good extent since then, despite the fact as feared and the evidence suggests, the demographic factors played a role in it[6,7]. The findings reveal, overall morbidity from cancer has decreased and net survival rates, both short-term and long-term, for all cancers combined have increased substantially in the past decades. The survival rates for cancer types that are responsive to therapy surpass 90% in developed countries, and the prognosis for several other cancer types that were considered the deadliest diseases earlier has improved noticeably in recent years thanks to rapid advances in clinical oncology [8.9]. However, the fight against cancer is far from over, as an estimation by the WHO in 2018 has revealed cancer incidence would be doubled to approximately 37 million new cases by 2040 with no confirmed remedy for most cancer types in the sight yet [10,11]. While researchers continue the endeavors to identify the exact causes of cancer types and subtypes and develop strategies for prevention, diagnosis, and treatment, cancer remains the leading cause of death and has a major impact on societies throughout the world. There are kinds of therapeutic options available now for cancer, such as chemotherapy, immunotherapy, hormonal therapy, and targeted drug therapy apart from

other forms of therapy that include radiation therapy, surgery, stem cell transplant, etc. One can receive a single type of treatment or a combination of therapies, but the treatment regimen must bring the much-needed cure that remains elusive in reality. It has also been observed that every patient responds differently to particular treatments despite having the same type and stage of cancer. These observations are compelling and have led researchers to look for a patient-specific treatment regimen necessitating the study of genetic features of the vulnerable candidates for the most effective treatment of cancer [12].

2. Cancer Genomics and the emergence of Precision Oncology

Rigorous cancer research in the past few decades supported by ongoing advances in cell and molecular biology has led scientists to clearly understand that there are genetic changes associated with cancer that cause the disease to grow and spread to other parts of the body. The fundamental abnormality resulting in cancer development is the unchecked proliferation of cells due to an absence of balance between cell divisions and cell loss through cell death and differentiation. Proliferation also requires a balanced rate of cell growth and division to maintain the increase in cell numbers. Division depends on cell cycle regulation that generally involves growth-regulatory signals as well as signaling proteins monitoring the genetic integrity of the cell to ascertain the developments go well in time [13]. It finally depends on progression through distinct phases of the cell cycle regulated by several cyclin-dependent kinases (CDKs) that act in association with their cyclin partners. Alterations in the overall expression pattern of cyclins lead the cellular process to go awry resulting in tumor formation. Most of the related events mainly depend on changes in the concerned genes, and the factors that cause these genetic changes often tend to provoke cancerous development [14]. Every single gene in the body is likely to have received mutations on varied occasions in the lifetime while the repair mechanism in place restricts the possible changes. In this way, the generation of cancer must be conclusively linked to the sustained deleterious changes in DNA sequence, i.e., gene mutations brought about by the external agents called mutagens resulting in the appearance of certain somatic variants and/or certain changes that might have been inherited to the body. Yet, a single mutation will not be enough to transform a normal cell into a cancer cell as it requires a number of changes to accumulate in the cells over time for cancerous development to take place. Mutations in the most pronounced cancer causing genes such as *RAS* or *MYC* will not lead to unchecked proliferation until the changes in repressor genes that essentially encode components of the protective mechanisms, such as retinoblastoma gene (*RB*) or the Tumor protein p53 (*TP53*) gene have not occurred alongside. Thus, multiple genetic changes will be required for cancer manifestation and so it can be seen as an evolutionary process involving both genetic change and selection [15]. There can be multiple rate-limiting steps working against the development of cancer along with persistent changes accelerating the process. Thus, most cancers are thought to derive from a single abnormal cell or a small group of cells with a few deleterious gene mutations followed by accumulation of additional changes in some of their descendants allowing them to outgrow others in number resulting in tumorous growth in the body [16].

Moreover, cancer can also be driven by epigenetic changes that alter the gene expression pattern of cells without the accompanying alteration in the cell's DNA sequence [17]. It is observed due to some physical modifications of chromatin structure capable of influencing the pattern of gene expression often led by DNA methylation, histone modifications and miRNA based alterations inside the cell often caused by sustained exposure of the affected cells to a few stressful external stimuli presented by certain environmental factors and/or lifestyle related changes that may involve nutrition, toxicants, alcohol, etc. [17]. Epigenetic changes will not alter the sequence of DNA, yet the process might cause point mutations and disable DNA repair mechanisms frequently involved in cancer development. Traditionally, epigenetic and genetic changes have been seen as two separate mechanisms participating independently in carcinogenesis which would not be the whole truth associated with cancer development. Recent studies from whole-exome sequencing (WES), the technique for sequencing all of the protein-coding regions of genes in a genome, for thousands of human cancers have revealed the presence of many inactivating mutations in genes that can potentially disrupt DNA methylation patterns, histone modifications, and nucleosome positioning and hence control the epigenome to contribute to cancer progression [18]. Thus, considering both the genome and epigenome regulate cancer progression through mutations, crosstalk between the two is anticipated and can be exploited to bring new possibilities to cancer treatment.

The range of cancer-causing mutations is known to be huge and the totality of cancer-causing mutations, regarded by researchers as the “mutational landscape”, differs from one another, depending on the type of cancer and even people suffering from the same cancer type are found to have considerably different mutation patterns. As routine work, scientists have been analyzing the mutational landscapes of different types of cancer, and the somatic structural variants (SVs) have been shown to account for more than half of all cancer-causing mutations. These are the variants or mutations different from the hereditary or germline variants, that have passed from parents to offspring and become incorporated into the DNA of every cell in the body. The somatic SVs can be noticed in the transformed cells and in their daughter cells that may continue to grow because of errors in DNA copying and their repair mechanisms during cell division thereby altering the genomic structure which will become more numerous with time. Although somatic SVs play a crucial role in cancer development, relatively little has been known about their mode of action in cancer development. Methods to detect and identify the functional effects of these SVs can enable researchers to understand the molecular consequences of individual somatic mutations in cancer. The findings related to the mutation-specific alterations could be used to develop therapies that target the mutated cells, opening up new possibilities in cancer therapy. Furthermore, most of the human genome consists of noncoding regions, and studies on variations in the noncoding regions of the cancer cells are revealing additional mechanisms underlying cancer progression. For example, changes in noncoding regions such as point mutations and complex genomic rearrangements can disrupt or create transcription factor-binding sites or even affect non-coding RNA loci leaving options for unwanted changes in the gene expression pattern of the cell. Ontogenesis typically involves interplay between germline and somatic variants and different modes of action of non-coding variants can further potentiate these developments. Thus, a systematic approach to unraveling the roles of noncoding genome in cancer progression could help improve cancer diagnosis and therapy [19,20].

Most important, the changes in vulnerable genes involved in cell growth, proliferation, death or differentiation appear to be the root cause of all the changes in cell behaviors and remain the most fundamental feature of all cancers, and so cancer is to be seen essentially as a genetic disease to be treated accordingly for better outcomes. Biometricians since the nineteenth century have been interested in decoding the relationship between genetics and diseases and attempted to understand the roles of "constitutional" and environmental factors in the distribution of diseases. The Werner Kalow's 1962 textbook 'Pharmacogenetics' published on the issue of heredity and the response to drugs, emphatically tried to set the agenda of relating the response of therapeutic drugs to their biochemistry and the role of genetics and evolution in shaping individual-level differences in and the idea seems to be of practical use in cancer research. The advances in genetic technologies and consequent understanding of clinically relevant genetic variations over the years are revolutionizing how a range of diseases can be diagnosed and treated in clinics exploiting genetic peculiarities of the individuals and it applies to cancer research adequately. It has been deliberated accordingly in recent years for cancer treatment leading to the emergence of precision oncology as the new field of cancer research that takes into account the genetic specificities of the individuals for a possible cure. [21]. Precision oncology is the term coined for clinical oncology practice that relies upon genomic profiling of the individual patient's tumor for a complete molecular characterization of the transformed cells and tissues to identify and target specific molecular alterations for efficient cancer therapy [22,23]. Thus, precision oncology seems to be a perfectly planned personalized medicine approach to cancer therapy that envisages bringing in custom-tailored treatment options for vulnerable individuals by designing a treatment regimen considering their unique needs for the best possible results. The proper use of precision oncology in clinics began approximately 25 years ago, but has noticeably enhanced the efficacy of cancer treatment and is on the verge of entering the mainstream of clinical practice [24,25].

3. Molecular Approach to Cellular Reprogramming and Cancer Treatment

Over the years, technological advances in the field of molecular biology have been exploited to fully understand the pathogenesis of human cancer. The emergence of next-generation sequencing (NGS) in 2005 has proved to be massively important in this direction as the technology is used to determine the order of nucleotides in entire genomes or targeted regions of DNA or RNA and has revolutionized biological research, allowing scientists to study biological systems at a level never tried before. It can provide new insights into the nature of genes and proteins thought to be associated with cancer, and the application of evolving molecular techniques to the study of cancer has also provided markers that have led to new advances in tumor diagnosis and proven to be immensely helpful in better assessment of prognosis and disease progression [26]. The important part of tumorigenesis is that cancers of different tissues utilize somewhat different patterns to finally converge to a common path of cancer development witnessed in the form of tumor growth followed by angiogenesis, invasion, and metastases. All such developments are ultimately guided by genetic and epigenetic changes associated with cancer cells and supported by certain tissue-specific factors that enable the tissue to exploit these

changes to its specific needs resulting in reprogramming of the molecular events utilized by different cancers, and so no gene change is thought to be common to all cancers [27,28].

Because the realization of uncontrolled cell growth and proliferation remain the most evident cause of cancer, certain alterations in the pattern of cell death and differentiation promoting overall cell survival could further aggravate the gradual transformation of tissue from normal to tumorous and from benign to metastatic. Certain disruptions of the physiologic balance between cell proliferation and cell death prolonging cell survival and proliferation are thought to be an important step in carcinogenesis. Expectedly, pieces of evidence confirm that the evasion of cell death by apoptosis and autophagy is the hallmark property of most, if not all cancers actively contributing to cell growth and proliferation. Apoptosis, the process of programmed cell death, also known as type 1 cell death, is mediated through caspase degradation activated by mitochondria. It is employed for removing damaged cells and is crucial to the early development and overall maintenance of tissue homeostasis. Loss of apoptotic control enables cancer cells to survive longer allowing more time for the accumulation of mutations which can deregulate cell proliferation and differentiation and stimulate angiogenesis and metastasis. Autophagy is the major intracellular degradation system mediated by lysosomes that involves the engulfment of unwanted proteins and damaged organelles in double-membraned vesicles called autophagosomes, for their destruction and recycling. Autophagy can play a protective role to promote cell survival, but excessive autophagy plays a suppressive role by inducing autophagic cell death, known as type 2 cell death. Autophagy has universally been accepted to play a tumor-suppressive role at the early stage, while defective autophagy is associated with tumorigenesis. Deregulation of these essential catabolic pathways contributes to the development of a tumor and is often involved in promoting invasion and metastasis. Cancer cells can develop novel mechanisms for evading apoptosis and autophagy and new discoveries direct toward the possible interrelationship between these two catabolic pathways. Evidence suggests that inhibition of apoptosis causes autophagy, while autophagy inhibition induces apoptosis. It may help the key proteins and intermediates involved with these pathways to be exploited in cancer therapeutics successfully.

An important feature of cancer is that the population of cells that make up cancer is profoundly heterogeneous at the genetic, and epigenetic levels, mainly because the cancer genome becomes unstable with accumulating numbers of cancer-causing gene mutations. [29,30]. There can be mutations present in the genes that further increase the inherent rate of genetic change, known as mutator mutations, that lead to greater genetic instability leading to the accumulation of multiple cancer-associated mutations within a cellular lineage at a rate that explains cancer manifestation at different stages in a lifetime. Mutator mutations and genetic instability are generalized concepts in cancer genetics, indicative of those few specific mutations that lead to an enhanced rate of single nucleotide substitutions within the gene sequence, and mutations that lead to microsatellite instability, chromosomal instability, and those affecting activities related to DNA damage and repair [31]. Furthermore, the gradual accumulation of oxidative damage to critical biomolecules such as DNA, due to persistent metabolic oxidative stress and inflammation also contributes to genomic instability and related diseases, including cancer indicating about appropriate measures for prevention and recovery. This feature of cancer

cells has also guided researchers to kill vulnerable cells by inducing lethal genomic instability in the cells through radiation therapy and chemotherapy. It has been a rather nonselective means of killing cancer cells with associated side effects which could be perfected by devising methods to selectively target the affected cells inside the body.

A crucial component of tissue heterogeneity found in tumors is cancer stem cells (CSCs), which are at the forefront of cancer research owing to their potential to induce cancer development. Recent studies have shown that there can be different subpopulations of CSCs within the tumor mass identified by cancer stem cell surface markers on normal stem cells with similar characteristics as normal stem cells, such as self-renewal and multilineage differentiation capabilities, with a much higher half-life than that of most other cells [32]. The intrinsic properties of self-renewal, multipotency, and longevity render stem cells more susceptible to accumulating gene mutations leading to neoplastic transformation, as proposed by the cancer stem cell hypothesis [33,34]. They have been found to be the key driver of tumorigenicity, tumor heterogeneity, recurrence, and drug resistance in many cancer types, and different targeted molecules, including nanoparticles-based drug delivery systems, are being tested for effectively targeting CSC related pathways for cancer treatment (Table 1) [35,36,37.38]. Moreover, the immune cells in the tumor mass could be hugely different, and an emerging finding of tumor heterogeneity is that tumors from different patients show a different degree of immune cell infiltration and immune cell composition. The immunologically "hot" tumors present elevated levels of T -cell infiltration, so these tumors are more susceptible to immunotherapy than immunologically "cold" tumors that don't allow similar T -cell infiltration. This immunogenic heterogeneity simply impacts treatment outcomes and may direct treatment planning [39,40].

Table 1: Stem Cell Marker (Soni et. al [35])

dvMarker Name	Cell Type	Significance	Reference
Nervous System			
CD133	Neural stem cell, HSC	Cell-surface protein Identifies neural stem cell Give rise to neurons & glial cells	[2]
GFAP (Glial fibrillary acidic protein)	Astrocyte	Produced protein	[3]

MAP-2 (Microtubule associated protein-2)	Neuron	Dendrite-specific MAP	[4]
Nestin	Neural progenitor	Intermediate filament structural protein expressed in primitive neural tissue	[5]
Noggin	Neuron	Neuron specific gene	[6]
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Pancreas			

CK19 (Cytokeratin 19)	Pancreatic epithelium	Identifies specific pancreatic epithelial cells that are progenitor for islet cells & ductal cells	[7]
Glucagon	Pancreatic islet	Expressed by alpha-islet cell of pancreas	[8]
Insulin	Pancreatic islet	Expressed by beta-islet cell of pancreas	[9]
PDX-1 (Insulin – promoting factor-1)	Pancreatic islet	Transcription factor expressed by beta-islet cell of pancreas	[10]
Nestin	Pancreatic progenitor	Structural filament protein indicative of progenitor cell lines	[11]
Pancreatic polypeptide	Pancreatic islet	Expressed by gamma-islet cell of pancreas	[12]
Blood Vessel			
Flk1 (fetal liver kinase-1)	Endothelial	Cell surface receptor protein, Identifies endothelial cell progenitor, Marker of cell-cell contact	[13]
Vascular endothelial growth factor	Endothelial	Endothelial cell proliferation	[14]
Bone			
BAP (Bone-specific alkaline phosphatase)	Osteoblast	Enzyme expressed in osteoblast, Activity indicates bone formation	[15]

Hydroxyapatite	Osteoblast	Mineralized bone matrix, Provides structural integrity, Marker of bone formation	[16]
(OC) Osteocalcin	Osteoblast	Mineral-binding protein uniquely synthesised by osteoblast, Marker of bone formation	[17]
Cartilage			
Collagen types II & IV	Chondrocyte	Structural proteins produced specifically by chondrocyte	[18]
Keratin	Keratinocyte	Principal protein of skin, Identifies differentiated keratinocyte	[19]
Liver			
Albumin	Hepatocyte	Principal protein, Indicates functioning of maturing & fully differentiated hepatocyte	[20]
B-1 Integrin	Hepatocyte	Cell-adhesion molecule important in cell-cell interaction, Marker expressed during development of liver	[21]
Bone Marrow & Blood			
BMPR (Bone morphogenic protein	Mesenchymal stem	Important for the differentiation of committed mesenchymal cell types	[22]

receptor)	&progenitor cells	from mesenchymal , BMPR identifies early mesenchymal lineages	
CD4 & CD8	White blood cell (WBC)	Cell-surface protein markers specific for mature T lymphocyte (WBC subtype)	[23]
CD34	Hematopoietic stem cell (HSC), Satellite, Endothelial progenitor	Cell-surface protein on bone marrow cell, Indicative of a HSC & Endothelial progenitor, CD34 also identifies muscle satellite	[24]
CD44	Mesenchymal	A type of cell-adhesion molecule used to identify specific types of mesenchymal cells	[25]
Fat			
ALBP (Adipocyte lipid-binding protein)	Adipocyte	Lipid-binding protein	[26]
Skeletal Muscle/Cardiac/Smooth Muscle			
MyoD& Pax7	Myoblast, Myocyte	Transcription factor, Directs differentiation of myoblasts into mature myocytes	[27]
Myosin heavy chain	Cardiomyocyte	A component of structural & contractile protein	[28]
Myosin light chain	Skeletal myocyte	A component of structural & contractile protein	[29]

Pluripotent stem cells			
Alakaline phosphatase	Embryonic stem (ES), Embryonic carcinoma (EC)	Elevated expression leads undifferentiation of pluripotent stem cells	[30]
AFP (Alpha-fetoprotein)	Endoderm	Expressed during development of primitive endoderm, Leads endodermal differentiation of pluripotent stem cell	[31]
CD30	ES, EC	Surface receptor molecule. Found on PSC	[32]
GATA-4 gene	Endoderm	Expression increases as ES differentiates into endoderm	[33]
NCAM (Neuronal cell adhesion molecule)	Ectoderm	Cell-surface molecule, Promotes cell-cell interaction, Indicates primitive neuroectodermformatiom	[34]
OCT4/POU5F1	ES, EC	Transcription factor, Essential for establishment & maintenance of undifferentiated PSCs	[35]
SOX2	ES, EC	Transcription factor, Essential for establishment & maintenance of undifferentiated PSCs	[36]
Pax6	Ectoderm	Transcription factor expressed as ES cell differentiates into neuro epithelium	[37]

Traditionally, cancer treatments such as chemotherapy and radiation therapy have been targeting actively growing cells of the tissue instead of just attacking diseased cells with a variety of side effects. So, the need for a deeper understanding of the molecular events underlying cancer progression was realized decades ago for developing treatments that would selectively target the affected cells alleviating the serious side effects of cancer treatment. The functional roles of many critical players involved in tumor growth, tissue invasion, and metastasis have been described precisely in past decades due to the draft of the human genome and other related developments that took place in the following years [41]. The findings have revealed many crucial genes and proteins related to pathways of cancer reprogramming as their deregulated results in cancer progression, and thus also presents attractive targets for cancer treatment. The *RB* and *TP53* are the central tumor suppressor genes that play central roles in regulating the cell cycle and are often found altered in many different cancer types. The RB gene product, i.e., Rb protein, forms complexes with the E2F family of transcription factors and down regulates several genes that code for key cell cycle regulators. Their transcriptional repression by the Rb-E2F complex can be relieved through phosphorylation of Rb leading to committed cell cycle progression which can be reversed afterward at the level of the cyclin-dependent kinases. TP53 gene that codes the proteinp53, a 53 kDa weighted nuclear protein, mainly acts to ensure genome stability, normal cell growth and proliferation. It is the key player in the tumor suppressive DNA damage response (DDR). The ATM (ataxia-telangiectasia mutated), ATR (ATM- and Rad3-Related), and other related protein kinases are the initial DDR kinases that help p53sense damage to DNA and activate other genes to repair the damage or suppress cell division to prevent accumulation of oncogenic mutations that often lead to tumor development in our body. The task is supported by p21, the cyclin-dependent kinase inhibitor (CKI) activated by p53, serving as a cell cycle inhibitor and anti-proliferative effector inside the cell. Stresses like a viral infection or DNA damage, a relatively common oncogenic act, will turn on p53 functions leading to cell cycle arrest for DNA repair, senescence for permanent growth arrest, or apoptosis for programmed cell death. A wide variety of mutations have been identified in p53 gene which often occurs late during cancer progression. Mutations in the gene not only disable their tumor suppressive function but can also engage in cancer-promoting activities by gaining oncogenic properties or inactivating remaining suppressive elements in the cell. An estimated 40-50% of human cancers carry deleterious mutations in the regulatory p53 gene [42].

The transcription factor NRF2 is the master regulator of the cellular antioxidant response, and studies have revealed many new roles for NRF2 in the regulation of essential cellular processes, though interacting with other pathways within the cells, thus establishing it as a truly pleiotropic transcription factor involved in carcinogenesis. Originally recognized as a target of chemo preventive agents to help prevent cancer, its protective role is found altered in 6-7% of cancer cases. A growing body of evidence has established the NRF2 pathway's involvement in the deregulation of cell metabolism, apoptosis, and self-renewal capacity of cancer stem cells, and thus an important driver of cancer progression, metastasis, and cancer drug resistance [43]. Similarly, the activation of the insulin-like growth factor receptor (IGF-IR) is an important factor in the growth, differentiation, and survival of cells in health and disease. IGF-IR plays an important role in the anchorage-independent growth of cells which enables cancer cells to survive and grow in the absence of anchorage to the extracellular matrix (ECM) and their

neighboring cells. It is closely involved in the regulation of pathways supporting cell growth and survival, cell cycle progression, angiogenesis, and metastatic activities in different cancers, and is considered essential in many cancers [44].

MYC genes are a group of related proto-oncogenes that code for Myc proteins, commonly involved in the pathophysiology of human cancer. Myc proteins alone may not cause the transformative effects, and studies reveal changes in the tumor suppressor gene such as *TP53* and *MYC* synergistically induce proliferation, survival, and metastasis. It is also a known target of RB repressor proteins deregulation of which may result in enhanced Myc activities. Myc has three family members, C-Myc, N-Myc, and L-Myc, which are essential transcription factors involved in the activation of a large number of protein-coding genes associated with many different biological processes including cell proliferation and differentiation, cell metabolism, and self-renewal of the stem cells. Myc oncoproteins have been shown to mandate tumor cell fate by inducing stemness and blocking differentiation and cellular senescence, the irreversible cell-cycle arrest contributing to cancer progression. Additionally, *MYC* can influence changes in the tumor microenvironment and induce activation of angiogenesis, and/or suppression of the host immune response. C-Myc oncoprotein forms a very crucial part of a dynamic cellular network whose members interact selectively with one another and with many of the transcriptional coregulators and histone-modifying enzymes supportive to maintain a sustained cell proliferation. C-Myc is constitutively and aberrantly expressed in over 70% of human cancers, with many of its target genes encoding proteins that initiate and maintain the transformed state [45].

The trimeric GTP-binding proteins (G proteins) attached to the cytoplasmic face of the plasma membrane are crucial in many cell processes and minor defects in signaling by these proteins can cause the pathophysiology of a disease. G-protein-linked receptors (GPCRs), are the serpentine transmembrane proteins that form the largest group of cell-surface receptors where the G proteins serve as the critical relay center coupling the receptors to different enzymes or ion channels in the membrane. There are different types of G proteins that associate specifically with a particular set of receptors in the plasma membrane to mediate responses to a variety of signaling molecules including hormones, neurotransmitters, and local mediators such as cytokines, chemokines, and growth factors. An activated receptor leads to the dissociation of the trimeric G protein stimulating its components in different ways, the GTP-binding protein subunit serves as GTPase which is crucial to GPCR signaling. Studies reveal they control many aspects of cancer progression including tumor growth, cell survival, invasion, migration, and metastasis. All GPCRs have a similar structure and the same mediator can activate many different receptors enabling them as the most likely targets for drug therapy. Noticeably about half of all known drugs actively target GPCRs and genomic studies continue revealing a growing number of new family members, many of which could prove to be potential targets for cancer therapy.

The small GTPase Ras protein belongs to the Ras superfamily of monomeric GTPases, which is a highly placed target in cancer therapy. They are the products of the most frequently mutated *RAS* genes in human cancers. Ras proteins are frequently involved in carrying signals from cell-surface receptors to different intracellular targets inside the cell It serves as a

transducer and bifurcation signaling protein capable of changing the properties of the signaling process by relaying it along multiple downstream pathways, including the signaling pathways reaching the nucleus to stimulate gene expression for cell proliferation. It is often required in receptor tyrosine kinase (RTK) activated signaling pathways involved in stimulating cell growth, proliferation and differentiation. Mammalian cells express three different yet closely related Ras proteins, K-Ras, H-Ras, and N-Ras, whose mutational activation effectively promotes oncogenesis. The mutation frequency of different Ras isoforms in human cancers varies, and K-Ras is the most frequently mutated isoform leading to tumor formation, invasion, and metastasis in many cancers [46]. The mutation rate for K-Ras is about 25% for all tumors but is found to mutate up to 80-90% in pancreatic ductal adenocarcinoma (PDAC) [47]. The treatment of PDAC, the commonest form of pancreatic cancer and a leading cause of cancer-related death, has so far been sparsely productive because of the tumor microenvironment, which possesses an ample amount of stromal cells and a complicated ECM. Genomic analysis has recently revealed that PDAC harbors frequently mutated genes that include *KRAS, TP53*, *CDKN2A,* and *SMAD4,* which can greatly influence the cellular processes and change the tumor microenvironment, which in turn, affects cancer progression. The drug development to block K-Ras has been partially successful like many other drugs, as the affected cells develop resistance to the inhibitors, a common problem encountered with drugs designed for cancer therapy [48,49]. The study of K- Ras resistance mechanisms reveal that researchers may have to try several different drug combinations to overcome resistance, and some of these are in the pipeline. Researchers are tirelessly working to target K-Ras and other signaling intermediates associated with cancer to develop novel therapeutic agents for different cancers.

B-cell lymphoma-2 (Bcl-2) protein is one crucial molecule that controls whether a cell lives or dies by blocking cell death by different means including apoptosis which may keep cancer cells from dying. It is a member of a family of regulatory proteins actively involved in the regulation of cell death by all major pathways, including apoptosis, autophagy, and necrosis, serving at the critical junction of multiple pathways with likely roles in oncogenesis. The Bcl-2 family proteins form subgroups, one of which may inhibit cell death and prolong cell survival through limiting apoptosis while others induce cell death by inducing apoptosis, autophagy, etc. [50]. The gene for the Bcl-2 protein is found on chromosome 18 but can be transferred to different chromosomes as can be seen in many cancer types. An increased expression of pro-survival proteins or abnormal reduction of death-inducing regulatory proteins, resulting in sharp inhibition of apoptosis and other related catabolic activities are frequently seen in many cancers. Resistance to apoptosis is a key development in several hematological malignancies and has been attributed to the up regulation of pro-survival Bcl-2 proteins. The important role played by Bcl-2 family proteins in cancer development renders them as potential targets for therapy of different cancers, including solid tumors and hematological disorders. Alterations in Bcl-2 activities with concurrent changes in other important regulators such as c-Myc or p53 appear to be great combinations in cancer progression [51]. The recent development of inhibitors of pro-survival Bcl-2 proteins, termed as BH3-mimetic drugs may prove to be novel agents for cancer therapy.

4. Signaling Pathway Deregulation and Prospective Targets for Cancer Therapy

Tumors and cancer are mainly the results of uncontrolled cell division. The root cause of cancer is usually genetic or epigenetic alterations in the affected cells leading them to grow and proliferate uncontrollably, although the progression of cancer remains dependent on a complex interplay between the tumor cells and surrounding non-neoplastic stromal cells and ECM present in the tumor microenvironment [52,53]. Cell division is ordinarily regulated by a group of extracellular growth factors, the proteins that cause resting cells to divide by exploiting the intrinsic regulatory process of the cell. Cell division is ordinarily regulated by a group of extracellular growth factors, the proteins that cause resting cells to divide by stimulating the intrinsic regulatory process of the cell. Cell signaling network as the foremost system of communication comes into consideration here as it involves many secreted protein receptors, growth factors, cytoplasmic proteins and kinases, and nuclear transcription factors, enabling individual cells to respond to extracellular signals with physiologically appropriate behavior. In this way, signaling pathways constitute an internal circuitry inside cells guided by external stimuli to help them sense whether their state of attachment to ECM and other cells is appropriate and if different growth factors, hormones, and cytokines guide them to proliferate or differentiate, move or stay put for now, or to commit to cell death by apoptosis or autophagy [54]. Cytokines ordinarily signal the immune cells to mount coordinated attacks on invading bacteria, and viruses and play essential roles in cancer prevention. Thus, signals propagated by growth factors and cytokines can simply tell individual cells to divide or not under particular conditions whose alterations could lead to the pathophysiology of cancer.

The earliest information regarding the relationship between cancer and growth factors came from the observation that normal cells in culture often required serum for proliferation, while cancer cells had a much less requirement for serum. The serum is known for providing growth factors among other ingredients needed for the overall regulation of the cell cycle. The other hints came from gene mutations found in cancer cells observed to cause changes in cell behaviors very similar to those related to the activities of growth factors and their receptors. The oncogenic mutations disrupt the cellular circuits that control cell adhesion and signaling, enabling cells that carry them to over-proliferate and invade the other tissues in an uncontrolled fashion. These mutations have been directly linked to the growth factors and their receptor proteins involved with tumor growth, angiogenesis, invasion, and metastases. Oncogenes are the mutated forms of cellular proto-oncogenes, normally involved in the regulation of cell growth, proliferation, and differentiation, as well as cell death, that translate into activated versions of signaling proteins leading to deregulation of the cell cycle and cell death (Table 2). Negatively acting tumor suppressor genes mostly act to repress growth and proliferative signals to maintain balance in product formation and are the actual targets for the action of many signaling molecules [55,56].

Table 2. Cancer Genes: Oncogenes and Tumor Suppressors in Different Cancer Types (https://www.cancerquest.org/cancer-biology/cancer-genes)

Oncogene Table

Oncogene	Function/Activation	Cancer*	References
ABL1	Promotes cell growth through tyrosine kinase activity	Chronic myelogenous leukemia	[27] [28]
AFF4/MLLT11	Fusion affects the MLLT11 transcription factor/methyltransferase. MLLT11 is also called HRX, ALL1 and HTRX1	Acute leukemias	[29] [30]
AKT2	Encodes a protein-serine/threonine kinase	Ovarian cancer	[31] [32]
ALK	Encodes a receptor tyrosine kinase	Lymphomas	[33] [34]
ALK/NPM	Translocation creates fusion protein with nucleophosmin(npm)	Large cell lymphomas	[35] [36]
RUNX1 (AML1)	Encodes a transcription factor	Acute myeloid leukemia	[37] [38]
RUNX1/MTG8(ETO)	New fusion protein created by translocation	Acute leukemias	[39] [40]
	Encodes a receptor		
AXL	tyrosine kinase	Hematopoietic cancers	[41] [42]
BCL-2, 3, 6	Block apoptosis (programmed cell death)	B-cell lymphomas and leukemias	[43] [44]
BCR/ABL	New protein created by fusion of bcr and abl triggers unregulated cell growth	Chronic myelogenous and acute lymphotic leukemia	[45] [46]

MYC (c-MYC)	Transcription factor that promotes cell proliferation and DNA synthesis	Leukemia; breast, stomach, lung, cervical, and colon carcinomas; neuroblastomas and glioblastomas	[47] [48]
MCF2 (DBL)	Guanine nucleotide exchange factor	Diffuse B-cell lymphoma	[49]
DEK/NUP214	New protein created by fusion	Acute myeloid leukemia	[50] [51]
TCF3/PBX1	New protein created by fusion	Acute pre B-cell leukemia; TCF3 also called E2A	[52] [53]
EGFR	Cell surface receptor that triggers cell growth through tyrosine kinase activity	Squamous cell carcinoma, glioblastomas, lung cancer	[54] [55] [56]
MLLT11	Fusion protein created by a translocation t(11;19).	Acute leukemias	[49] [57]
ERG/FUS	Fusion protein created by t(16:21) translocation. The erg protein is a transcription factor.	Myeloid leukemia	[58] [59]
ERBB2	Cell surface receptor that triggers cell growth through tyrosine kinase activity; also known as HER2 or neu	Breast, salivary gland, and ovarian carcinomas	[60] [61]
ETS1	Transcription factor	Lymphoma	[62] [63]
EWSR1/FLI1	Fusion protein created by t(11:22) translocation.	Ewing Sarcoma	[64] [65]

CSF1R	Tyrosine kinase	Sarcoma	[66] [67]
FOS	Transcription factor for API	Osteosarcoma	[68] [69]
FES	Tyrosine kinase	Sarcoma	[70] [71]
GLI1	Transcription factor	Glioblastoma	[72] [73]
GNAS (GSP)	Membrane associated G protein	Thyroid carcinoma	[74] [75]
HER2/neu	Overexpression of signaling kinase due to gene amplification	Breast and cervical carcinomas	[76] [77]

TLX1	Transcription factor; aka HOX11	Acute T-cell leukemia	[78] [79]
FGF4	Encodes fibroblast growth factor; aka HST1	Breast and squamous cell carcinomas	[49]
IL3	Cell signaling molecule	Acute pre B-cell leukemia	[49]
FGF3 (INT-2)	Encodes a fibroblast growth factor	Breast and squamous cell carcinomas	[49]
JUN	Transcription factor for API	Sarcoma	[80] [17]
KIT	Tyrosine kinase	Sarcoma	[80] [17]

FGF4 (KS3)	Herpes virus encoded growth factor	Kaposi's sarcoma	[17]
K-SAM	Fibroblast growth factor receptor	Stomach carcinomas	[49]
AKAP13	Guanine nucleotide exchange factor; aka LBC	Myeloid leukemias	[17] [81]
LCK	Tyrosine kinase	T-cell lymphoma	[17]
LMO1, LMO2	Transcription factors	T-cell lymphoma	[17]
MYCL	Transcription factor	Lung carcinomas	[49] [80]
LYL1	Transcription factor	Acute T-cell leukemia	[49]
NFKB2	Transcription factor. Also called LYT-10	B-cell lymphoma	[17]
NFKB2/Cα1	Fusion protein formed by the (10;14) (q24;q32) translocation of NFKB2 next to the C alpha 1 immunoglobulin locus.		[49]
MAS1	Angiotensin receptor	Mammary carcinoma	[17]
MDM2	Encodes a protein that inhibits and leads to the degradation of p53	Sarcomas	[49] [80]

MLLT11	Transcription factor/methyltransferase (also called HRX and ALL1)	Acute myeloid leukemia	[82] [17]
MOS	Serine/threonine kinase	Lung cancer	[49] [83]
	Fusion of transcription repressor to factor to a		

RUNX1T1	transcription factor. Also known as MTG8 and AML1-MTG8	Acute leukemias	[49]
MYB	Transcription factor	Colon carcinoma and leukemias	[49]
MYH11/CBFB	New protein created by fusion of transcription factors via an inversion in chromosome 16.	Acute myeloid leukemia	[49]
NEU	Tyrosine kinase. Also called ERBB2 or HER2	Glioblastomas, and squamous cell carcinomas	[84] [49]
MYCN	Cell proliferation and DNA synthesis	Neuroblastomas, retinoblastomas, and lung carcinomas	[84] [49]
MCF2L (OST)	Guanine nucleotide exchange factor	Osteosarcomas	[17]
PAX-5	Transcription factor	Lympho-plasmacytoid B-cell lymphoma	[17]
PBX1/E2A	Fusion protein formed via t(1:19) translocation. Transcription factor	Acute pre B-cell leukemia	[49]
PIM1	Serine/threonine kinase	T-cell lymphoma	[17]

CCND1	Encodes cyclin D1. Involved in cell cycle regulation. Also called PRAD1	Breast and squamous cell carcinomas	[49]
RAF1	Serine/threonine kinase	Many cancer types	[49]
RARA/PML	Fusion protein caused by t(15:17) translocation. Retinoic acid receptor.	Acute premyelocytic leukemia	[84] [49]
HRAS	G-protein. Signal transduction.	Bladder carcinoma	[49]
KRAS	G-protein. Signal transduction	Lung, ovarian, and bladder carcinoma	[49] [80]
NRAS	G-protein. Signal transduction	Breast carcinoma	[49]
REL/NRG	Fusion protein formed by deletion in chromosome 2. Transcription factor.	B-cell lymphoma	[49] [80]
RET	Cell surface receptor. Tyrosine kinase	Thyroid carcinomas, multiple endocrine neoplasia type 2	[84] [49]
RHOM1, RHOM2	Transcription factors aka LMO1 and LMO2	Acute T-cell leukemia	[49]
ROS1	Tyrosine kinase	Sarcoma	[17]
SKI	Transcription factor	Carcinomas	[17]
SIS (aka PDGFB)	Growth factor	Glioma, fibrosarcoma	[17]
SET/CAN	Fusion protein formed by rearrangement of chromosome 9. Protein localization	Acute myeloid leukemia	[17] [85]
SRC	Tyrosine kinase	Sarcomas	[49] [86]
TAL1, TAL2	Transcription factor.TAL1 is also	Acute T-cell leukemia	[49] [87]

	called SCL		
NOTCH1 (TAN1)	Altered form of Notch (a cellular receptor) formed	Acute T-cell leukemia	[49] [88]

TIAM1	Guanine nucleotide exchange factor	T-lymphoma	[17] [89]
TSC2	GTPase activator	Renal and brain tumors	[17] [90]
NTRK1	Receptor tyrosine kinase	Colon and thyroid carcinomas	[49] [91]

Tumor Suppressor Table

Tumor Suppressor	Function	Cancer *	References
APC	Controls the function of specific transcription factors which are involved in tumorigenesis, and development and homeostasis of some cell types including epithelial and lymphoid cells. APC has also been implicated in cell proliferation and other cellular activities such as migration, and adhesion.	Familial adenomatous and non-inherited colorectal carcinomas	[121] [122]
BRCA1, BRCA2	DNA Damage Repair	Inherited breast cancers; ovarian	[123]

		cancers	
CDKN2A	Gene locus that encodes the tumor suppressors p16 and p14ARF.	Brain tumors	1 [124]
DCC	Netrin-1 receptor. Regulation of cell proliferation and apoptosis of intestinal epithelium.	Colorectal carcinomas	[125] [126] [127]
DPC4 (aka SMAD4)	Transciptional factor involved in development; Implicated in metastasis and tumor invasiveness.	Colorectal tumors, pancreatic neoplasia	[128] [129]
MADR2 (aka SMAD2)	Mediates signaling from growth factor receptors. Assists in transport of SMAD4 into nucleus.	Colorectal cancer	[130] [131]
MEN1	Codes for the menin protein that interacts with transcription factors, DNA repair proteins, cytoskeletal proteins and others. Function not clearly defined.	Multiple endocrine neoplasia type 1	[132]
CDKN2A (aka MTS1)	Inhibitor of cyclin-dependent kinases; regulates cell cycle passage from G1 into S.	Melanomas	[133]
NF1	RAS GTPase activating protein (RAS-GAP)	Neurofibromatosis type 1	[134]

NF2	ERM protein; organize plasma membrane by assembling protein complexes and linking them to actin.	Neurofibromatosis type 2	[135]
	Encodes a transcription	Bladder, breast,	
TP53 (often just p53 in older articles)	factor for p21, a protein that arrests the cell cycle in G1 phase. p53 integrates signals related to cell size, DNA integrity and chrommosome replication.	colorectal, esophageal, liver, lung, prostate, and ovarian carcinomas; brain tumors, sarcomas, lymphomas, and leukemias	[136]
PTEN	Lipid phosphatase. Regulates cell survival	Cowden syndrome; increased risk of breast and thyroid cancer	2 [137]
RB1	Binds to, and inhibits, the E2F transcription factor. Halts cell cycle progression	Retinoblastoma, sarcomas; bladder, breast, esophageal, prostate, and lung carcinomas	[138]
VHL	Cell cycle regulation. May increase stability and activity of p53	Renal cell carcinomas	1 [139]
WRN	DNA helicase and exonuclease. Involved in repair of DNA breaks.	Werner syndrome	2 [140]
WT1	Transcription factor. Essential role in development.	Wilms tumors (pediatric kidney cancer)	1

* The cancer types listed in this column are those that are predominantly associated with each tumor suppressor gene but this is not an exhaustive list.

A critically important finding of cell signaling is that one kind of cell membrane receptor can mediate many different downstream intracellular pathways and one pathway can also be activated by several of the upstream surface receptors revealing common signaling components in multiple signaling pathways. For example, the RTKs, like Epidermal growth factor receptor (EGFR), Fibroblast growth factor receptor (FGFR), Insulin-like growth factor receptor (IGFR), Vascular endothelial growth factor receptor (VEGFR), Platelet-derived growth factor receptor (PDGFR), and the GPCRs, can all activate the MAPK cascade while the widely studied RTKs such as EGFR/HER family receptor can initiate different signaling pathways including mitogen-activated protein kinase (MAPK), phosphoinositide-3-kinase (PI3K)/AKT, and mammalian target of rapamycin (mTOR) pathways involved in regulations of cell growth, proliferation, differentiation, and survival. This feature of the signaling processes presents an option for crosstalk between components of many different signaling pathways at different stages of the processes whose alterations could swiftly lead to cancer manifestation. As generally observed, most of the cell signaling pathways contribute to the development of cancer and, seldom does a cancer type arise from the deregulation of a single pathway. Breast cancer can arise due to elevated expression of estrogen receptor (ER), EGFR/HER, or IGFR, but on many occasions, more than one of these pathways may be deregulated. As a matter of fact, signal transduction leading to tumor growth, cancer cell migration, metastasis, and drug resistance are often complex processes, as cancer cells can develop abnormalities in multiple pathways or rely on the crosstalk between different signaling pathways and on redundant pathways for growth and survival (Fig. 1) [57].

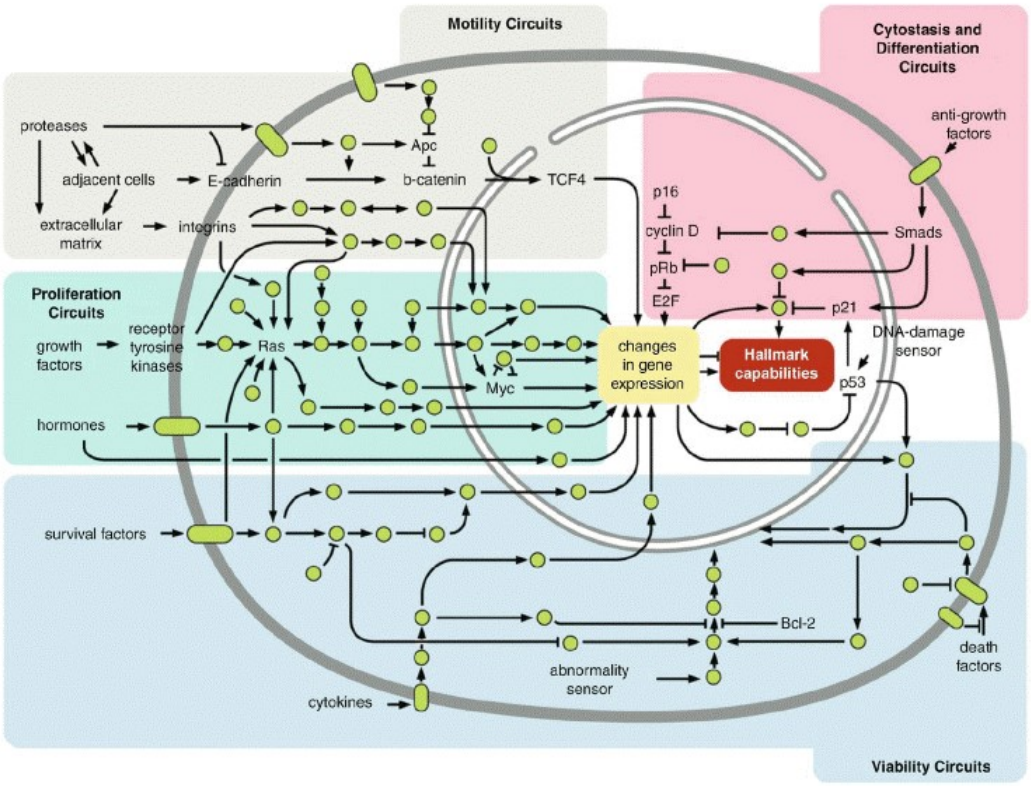

Figure 1. Intracellular Signaling Networks Regulate the Operations of the Cancer Cell.

An elaborate integrated circuit operates within normal cells and is reprogrammed to regulate hallmark capabilities within cancer cells. Separate sub-circuits, depicted here in differently colored fields, are specialized to orchestrate the various capabilities. At one level, this depiction is simplistic, as there is considerable crosstalk between such subcir- cuits. In addition, because each cancer cell is exposed to a complex mixture of signals from its microenvironment, each of these sub-circuits is connected with signals originating from other cells in the tumor microenvironment. (Hanahan and Wienberg [57].)

As cancer progression generally involves alterations in signaling pathways due to mutations in the concerned genes, it is convincingly satisfying to consider that therapeutic intervention that takes into account this biology of the affected cells will pave the way for the most effective treatment of cancer (Fig. 2) [58,59]. Therefore, therapeutic substances that target the signal transduction process are being explored as prospective and efficacious agents for cancer treatments. It has been established in clinical practice, although, that targeting a single intermediate or pathway effectively brings considerable results toward recovery, possibly because it impedes the synergistic signaling process of disease progression, but the constitutive activation of a molecular target that contributes to cancer developments can be sustained by different mechanisms, and strategies that inhibit multiple targets or redundant pathways simultaneously with molecular-targeted agents should prove to be even more effective way to

treat cancer and overcome resistance in cancer therapy [60]. The representative signaling pathway involved in cancer cell reprogramming and the scope for targeting the signaling intermediates for efficient management of the disease are being discussed here in brief.

Ras/Raf/MAPK signaling pathway: Mitogen activated protein kinase (MAPK) signaling cascade is the key signaling pathway in the regulation of normal cells. This pathway is the main route for extracellular growth factors to transmit signals to the cell that regulate a wide variety of cellular processes including cell proliferation, differentiation, apoptosis, and stress response and abnormalities in this pathway are common in many cancer types [61]. MAPK cascades comprise the mitogen-activated protein kinases (MAPKs), regarded as extracellular signal-regulated kinases (ERKs), MAPK/ERK protein kinase (MEK), and rapidly accelerated fibrosarcoma (Raf) kinases. Importantly, the Raf/MEK/ERK signaling pathway is a key downstream effector of Ras GTPase protiens. It may act as molecular switch that control the activation and regulation of related cellular pathways responsible for different cell behaviors critical to cancer development [62]. Furthermore, the mutational activation of Raf in human cancers supports the important role of this pathway in oncogenesis. ERK is a downstream component of an evolutionarily conserved signaling system that is activated by MEK followed by its activation by Raf activated by Ras in response to the extracellular signals. Activated ERK relays the signal downstream to the gene regulatory proteins resulting in the expression of the target genes and it has been the subject of intense scrutiny in the treatment of cancer. Growth factor receptors, such as the TGF-β receptors, EGFR, VEGFR, PDGFR, FGFR, and IGFR, can all activate Ras ultimately leading to ERK activation. The study with selected inhibitors against the targets in this cascade has shown positive results, such as growth inhibition, anti-angiogenesis, and suppressed metastasis in cancer cell lines and animal models. These results reveal that this strategy is effective at inhibiting cancer cell proliferation and survival, and more clinical trials and validation is ongoing for efficacious treatment of the disease [63].

PI3K/Akt/mTOR signaling pathway: The PI3K/Akt/mTOR pathway is activated by a variety of factors, such as cytokine receptors, GPCRs, RTKs, and integrins, and regulates several cellular and metabolic activities that lead to cell growth and survival. Phosphatidylinositol (PI) is a unique membrane lipid phosphorylated by activated, PI 3-kinase to generate phosphatidylinositol-3,4,5-triphosphate [PI (3,4,5) P3] that works as the docking site for intracellular signaling proteins bringing the proteins together into signaling complexes. The main PI3K effector Akt, also called protein kinase B (PKB) is activated in the process that regulates different downstream targets including mTOR, to relay the signals through the cell. The kinase protein mTOR is of particular interest as it works as a master regulator of cellular processes involved in cell growth, proliferation, autophagy, and apoptosis, by participating in multiple signaling pathways inside the cell. The canonical pathway of mTOR activation depends on signaling through PI3K/Akt, though alternative non-Akt dependent activation through the MAPK pathway is now recognized as well. Activated mTOR can assemble into a variety of complexes to catalyze the phosphorylation of multiple targets, including Akt), protein kinase C (PKC), components of the insulin-like growth factor receptor (IGF-IR) signaling, and the protein

synthesis machinery to influence the cell behaviors accordingly. Persistent mutational activation of the PI3K/Akt/mTOR pathway in the absence of different stimuli has been frequently observed in many cancers. Adaptive resistance to the pathway inhibitors is common, and combination therapy, if well tolerated, may produce favorable anticancer results [64,65]. Several mTOR inhibitors have been developed so far to treat cancer, and some are being evaluated in clinical trials for approval [66,67].

Wnt/β-catenin signaling pathway: This signaling is one of the key signaling cascades involved in the regulation of cell growth and cell polarity in the developmental process, and has been typically associated with stemness, and implicated in carcinogenesis. The signaling pathway begins with a Wnt ligand binding to the extracellular domain of a Frizzled (Fz) family receptor, a distinct family of GPCRs to relay signals through the cell via different paths influencing a variety of cellular mechanisms critical to cancer development. Wnt pathway has been formally divided into the β-catenin dependent canonical pathway and the β-catenin independent, non-canonical Planar cell polarity (PCP) signaling pathway, and Wnt/calcium pathway. The canonical Wnt signaling is a genetic pathway that promotes normal cell growth requiring meticulous control of a tumor suppressor gene called adenomatous polyposis coli(APC), which functions to limit the activation of β- catenin preventing excessive cell growth and tumor formation. The APC/β-catenin pathway is a highly regulated process that involves many different proteins. APC itself is a negative regulator, a Wnt antagonist that binds to a variety of proteins that include β- catenin. It is an essential component of the cytoplasmic protein complex that targets β-catenin for proteasomal destruction. Furthermore, MYC and cyclins are the important transcriptional targets of this pathway, indicatingan overlap with several tumor-promoting pathways. Mutations that prevent the degradation of β-catenin, including certain mutations in β-catenin or the APCcomponent of the β-catenin destruction complex and others, distort theregenerative pathway to contribute to cancer progression and metastasis [68].Deregulation of the signaling pathway results in alterations in cell growth andsurvival, maintenance of cancer stem cells, metastasis, and immune control which have been linked to both solid and hematological tumors. The activation of the non-canonical pathway involves the recruitment of small GTPase activation thatleads to enzymatic rearrangements of the cytoskeleton and/or certaintranscriptional activation of effector proteins. The Wnt/Ca2+ signaling isfollowed by G-protein-activated phospholipase C activity leading tointracellular calcium fluxes and downstream calcium-dependent cytoskeletal rearrangement and/or transcriptional responses. The Wnt signaling pathway is a crucial mediator in maintaining tissue homeostasis, stem cell populations for tissue repair, and wound healing and is frequently involved in the incidences of many cancer types.Its role in immune evasion and drug resistance is well recognized, andidentifying tumor-specific signaling intermediates as targets for drug action may be crucial to cancer therapy. Many different agents effectively targetingthe molecules of signaling pathways are being explored for the efficacious treatment of different cancers [69,70].

Hedgehog (Hh) Signaling Pathway: Hh is an evolutionarily conserved signaling pathway of transporting signals from the cell surface to the nucleus and is one of a few signaling pathways that is frequently used for intercellular communication. It is a key regulator of embryonic development that controls cell patterning, proliferation, and differentiation for the organogenesis of all the organs in mammals as well as in the regeneration and maintenance of tissue homeostasis The pathway has and has been implicated in birth defects, tissue regeneration, stem cell renewal, and cancer. Constitutive activation of the Hh performs its tasks through a signaling cascade in a context-dependent manner to regulate the change of balance between activator and repressor forms of the glioma-associated oncogene (Gli) transcription factors. The activated form of Gli moves to the nucleus to bind to their promoters leading to the transcription of the target genes. Hh signaling pathway is associated with several cancers and communication between Hh and major signaling pathways, such as Wnt, Notch, and TGF-β, play crucial roles in the development, homeostasis, and pathophysiologies of diseases. The aberrant activation of the Hh signaling pathway, caused by the excessive expression of the Hh signaling molecules can be attributed to mutations in the related genes. Several Hh signaling pathway inhibitors have been developed for a range of different cancers. A few agents are thought to be highly effective for patients with recurrent and advanced cancers.

Notch signaling pathways: Notch signaling is associated with the regulation of many cellular processes like cell proliferation, survival, and differentiation through cell-to-cell communication crucial to the development of many tissues and cell types. The signaling pathway is a key regulator of self-renewal and differentiation of the cell and is known as an important regulator of Hematopoiesis. Notch is thought to be a binary cell-fate-determining pathway, and has been implicated in the context-dependent oncogenic stimulation of many solid and hematological cancers. Activation is followed by cleavage of Notch producing Notch intracellular domain (NCID) which translocates to the nucleus where it regulates gene expression involved in the control of cell proliferation, survival, and differentiation [71]. Both Hh and Notch signaling pathways are the active regulators of communication between cells and are critical to organ development, regeneration, maintenance of stem cells, and tissue homeostasis. The emergence of cancer stem cells (CSCs) as tumor-initiating cells with self-renewal potential in cancer progression further supports the role of these signaling pathways in maintaining CSCs in the tumor mass causing disease recurrence and chemoresistance [72]. The Hippo pathway has been found to repress Wnt signaling stimulating which may induce cancer stems while the alterations in Wnt signaling are known to influence Hg and Notch pathways alternatively which can be intrinsically related to the maintenance of cancer stem cell properties. Thus, the components of one signaling pathway could influence the performance of the other pathways to synergistically maintain the activities of CSCs involved in cancer development. It allows the opportunities to identify the intermediates with confirmed hyperactivities as potential targets in anti-CSC drug discovery for effective cancer treatment [73]. Selective targeting of these pathways along with other proliferatary pathways such as the PI3K/Akt or RAS/RAF/MAPK pathways could prove to be an effective strategy for combinatorial drug therapy of cancer [74,75].

JAK/STAT signaling pathway: The Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling pathway, is actively involved in the regulation of essential cellular activities, such as proliferation, survival, invasion, inflammation, and immunity deregulation of which has been associated with cancer progression and metastasis. There are seven different signal transducers and activators of transcription (STAT) family proteins in mammals, STAT 1, 2, 3, 4, 5A, 5B, and STAT 6. The Janus kinases (JAK) family comprises four different members, JAK1, 2, 3, and Tyk (tyrosine kinase). This pathway largely involves cytokine signaling which is closely related to the activities of T and B cells and so often linked to the development of hematological malignancies. When a cell is exposed to cytokines such as interleukin-6 (IL-6) or interferon-gamma (IFN-g), JAK kinases associated with the cytokine receptors are activated to phosphorylate and activate STATs. STAT family members, especially STAT3 and STAT5, are involved in cancer progression, whereas STAT1 plays the opposite role by suppressing tumor growth. Target genes of STAT5 may regulate processes such as cell cycle progression, survival, and self-renewal, via binding to growth factors and cytokines and constitutive activation of the pathway leads to the high-level expression of genes and proteins, resulting in different forms of cancer manifestation [76,77]. It could be finally mediated through the suppression of p53 activities or crosstalk with NF-kB signaling or expression of the Runt-related transcription factors (RUNX) family proteins, leading to inflammation and cancer [78]. Activation of the JAK/STAT pathway can be controlled by suppressors of cytokine signaling (SOCS) family proteins while other inhibitory proteins and phosphatases may also contribute to inhibiting the activated state. The upregulation of JAK/STAT proteins, as well as the reduction of the different SOCS proteins, are associated with different malignancies including solid tumors. This signaling pathway has also been associated with the development of tumor tolerance as hyperactivation of the pathway often leads to an increase in gene expression resulting in enhanced activity of the regulatory T cells (Tregs), a specialized subpopulation of T cells that work to limit T cell proliferation and cytokine production, thereby resulting in suppression of immune response and maintenance of self-tolerance. These specificities of the signaling pathway provide options for effective drug development against the pathway intermediates with fewer side effects. Many JAK and STAT inhibitors have been tested for their efficacy in cancer treatment and a few inhibitors have shown to be clinically relevant. Targeting the JAK/STAT signaling pathway efficiently remains an intriguing strategy in cancer therapy [79,80].

The NF-κB signaling Pathay: This is initiated by the degradation of IκB proteins via IκB kinase (IKK). IkB binds to the NF-κB dimer in the resting state, preventing it from binding DNA, and its degradation leads to the activation of NF-κB and consequent transcriptional activation. The signaling is mediated via both the canonical (NEMO-dependent) pathway and the noncanonical (NEMO-independent) pathway. The canonical pathway is thought to be involved in immune responses and immunosurveillance, while the noncanonical pathway is associated with developmental activities. Thus, canonical and noncanonical pathways have generally been taken

to be distinct, but studies have revealed numerous crosstalk mechanisms that connect them, so both pathways may result in a single NF-κB system [81]. Constitutively activated NF-κB signaling may lead to inflammation-related disorders, and its role in pathological inflammation and cancer development is well recognized now [82.83]. Furthermore, NF-κB signaling is associated with the epithelial-mesenchymal transition (EMT), which occurs frequently during tumor progression and metastasis. E-cadherin is a well-known tumor suppressor protein, and the regulation of the adhesive activity of E-cadherin present at the cell surface is important in cancer, and its repression by NF-κB is attributed to EMT induction. NF-kB has been implicated in EMT and metastasis also through the activation of EMT master-switch transcription factors and is highly invasive [84]. Evidence suggests that reversal of EMT is triggered by inhibition of NF-kB signaling, but the activated NF-κB pathway may contribute to antiapoptotic activation, ECM degradation, and E-cadherin-mediated EMT, which results in tumor growth, invasion, and metastasis. NF-κB signaling molecules also communicate with many other signaling pathways as crosstalk can be mediated by intermediates, such as STAT3 and, GSK3-β, p53, p38, PI3K, or the proinflammatory TGF-β proteins which modulate NF-κB transcriptional activity [85,86]. Thus, targeting the NF-κB signaling pathway represents an attractive approach to anti-inflammatory and anticancer therapies, and inhibitors have been developed to block different steps of NF-κB signaling for cancer treatment [87,88].

The cGAS-STING pathway: The cyclic GMP–AMP synthase (cGAS)-stimulator of interferon genes (STING) signaling pathway represents a key cellular process that controls inflammatory responses in the presence of foreign particles based on dsDNA recognition through pattern recognition receptors (PPRs) and thus regulates the overall preparedness for the cell to withstand adversity caused by infection or injury. The binding of cGAS to double-stranded DNA (dsDNA) induces the catalytic activity of the synthase and leads to the production of 2′3′ cyclic GMP–AMP (cGAMP), a second messenger molecule that quickly binds to the stimulator of interferon genes (STING) dimers localized at the endoplasmic reticulum (ER) membrane, which is then released to undergo further processing, finally resulting in the expression of type I interferons, interferon-stimulated genes (ISGs), and several other inflammatory mediators, pro-apoptotic genes and chemokines. STING also binds and stimulates IKK, triggering the transcriptional activation of NF-kB that pro- motes noncanonical NF-κB responses. This signaling outcome limits type I interferons and the canonical NF-κB pathway as critical, negative regulators of STING effector mechanisms, which can have important biological consequences related to immune evasion and metastasis [89,90]. cGAS–STING signaling may also induce autophagy and additionally communicate via p53, MAPK p38, and STAT3 signaling in a context-dependent manner. This finding reveals the complex role of this signaling in the regulation of cell behaviors. Mutations associated with the pathway have been implicated in cancer progression. cGAS-STING is an important pathway in cancer immunotherapy, and inhibitors of the pathways are being tried for targeted drug therapy [91,92].

The Hippo signaling Pathway: This pathway is an evolutionarily conserved major signaling network that controls contact inhibition and organ size development, and its deregulation has been implicated in many cancer types. Contact inhibition enables normal cells to cease growth and proliferation when in contact with each other and an absence of this property can lead the affected cells to proliferate uncontrollably resulting in a malignant growth. The canonical Hippo pathway comprises of a kinase cascade and related regulators that together work as a repressive system involving phosphorylation and inhibition of the two transcription coactivators YAP and TAZ, as the downstream effectors to execute its role in the regulation of organ size and tissue homeostasis. Phosphatase and protein ubiquitination modulate the activities of the coactivators in the cascade and can also be regulated by the cytoskeleton for its role in the signaling process. When dephosphorylated, YAP/TAZ translocate into the nucleus and interacts with other transcription factors to induce gene expression leading to cell proliferation and inhibition of apoptosis. The regulation of YAP1/TAZ may be influenced by many other molecular events, including crosstalk with Wnt/β-catenin signaling, and is mostly oncogenic. The core activity of this pathway is controlled by cell density, polarity and energy requirements as well as ECM stiffness and shear stress, which together can regulate contact inhibition and related developments, and so its activities can be regulated at multiple levels and widely implicated in angiogenesis and chemoresistance [93]. Cell proliferation and stem cell self-renewal can be directly attributed to contact inhibition governed by this signaling pathway. The noncanonical Hippo pathway operates in tight and adherens junction complexes to control their localization and activity within the cell. Several studies suggest that an overexpression of the components of the Hippo pathway contributes to aberrant cell cycle regulation leading to cancer development. The exact role of the Hippo pathway in cell cycle regulation has not been thoroughly understood, but an in-depth exploration of the process could provide effective therapeutic options for cancer treatment. The properties of the extracellular signaling and membrane receptors involved with the pathway remain to be fully known, yet drugs targeting the components of this pathway are under investigation for their efficacy in cancer therapy [94.95].

TGF-β/SMAD signaling pathway: Transforming growth factor beta (TGF-β) superfamily proteins serve as multifunctional secreted cytokines whose activities may be deregulated in many diseases, including cancer. TGF-β signaling is known to control many different biological processes, including cell proliferation, differentiation, migration, and apoptosis, and plays context-dependent roles in carcinogenesis. SMAD proteins are the main signal transducers for the canonical pathway of TGF-β signaling. It comprises a family of structurally similar and well-conserved transcription factors which can relay extracellular signals directly to the nucleus and are critically important for regulating cell development and growth. TGF-β initially functions as a tumor suppressor through the SMAD-mediated pathway when TGF-β/SMAD-dependent p15/p21 induction or c-MYC suppression works well to maintain growth arrest, cell differentiation, and apoptosis. However, the situation could be the opposite if SMAD- dependent suppression became ineffective under the influence of certain oncogenic mutations mediated by

many other pathways, and the role of TGF-β could become antiapoptotic, EMT inducer, and carcinogenic. SMAD inactivation under such a circumstance convincingly explains the situation-based role of TGF-β in different cancers. Furthermore, the classical, SMAD-independent pathway of TGF-β receptors may involve crosstalk with other signaling pathways, such as Wnt/β-catenin, Ras/RAF/MAPK, and PI3K/Akt/mTOR pathways, to play a role in carcinogenesis, and a proper understanding of the TGF- β signaling pathway in cancer progression would resolve controversies related to the signaling pathways [96,97]. The vast range of functionality associated with TGF-β during cancer progression is evidently clear now and it has led to the development of multiple therapeutic agents targeting different intermediates of the signaling pathway, and a combination of drugs may produce even better results against reoccurring and metastasizing cancer [98,99].

5. The Cancer Genome Atlas (TCGA) Program

The Cancer Genome Atlas (TCGA) Program, the landmark cancer genomics program initiated by the National Institute of Health (NIH), has contributed immensely to realizing the importance of genomics in cancer research and treatment in the last decade and has begun to change the way the disease has been treated in the clinic. It has been a joint effort by the National Cancer Institute (NCI) and the National Human Genome Research Institute (NHGRI), both part of the NIH, that started working in 2006 and brought together researchers from diverse disciplines and multiple institutions to work on the characterization and analysis of cancer at the molecular level for a complete understanding of the genetic basis of human cancer [100,101]. The TCGA Research Network has profiled and analyzed a large number of human tumors to discover molecular aberrations at the DNA, RNA, protein, and epigenetic levels and has been providing markers for different cancer types since then and thus forms the basis of precision oncology in relity.. A vast number of mutations contribute to cancer and the use of next-generation sequencing-based approaches in clinical diagnostics is leading to a tremendous increase in data with an enormous number of variants of uncertain significance requiring further analysis and validation by means of accurate techniques to fulfill the purpose involved satisfactorily [102,103]. Predicting the effects of mutations using in silico tools has become a frequently used approach, but these data cannot be analyzed by simply using traditional tools and techniques that have been available to scientists, but even more advanced computational methods are supposed to be coming to better understand the molecular basis of the origin and evolution, of cancer. To meet this end, a cancer hallmark framework through modeling genome sequencing data has been proposed for the systematic identification of representative driver networks to convincingly predict cancer evolution and associated clinical phenotypes [104,105]. It is based on the consideration that possible observable combinations of those mutations must converge to a few hallmarks signaling pathways and networks responsible for cancer manifestation. Thus, it aims to analyze the data to explain how the different gene mutations in different patients bring the same downstream effects on the protein networks, ultimately leading to the common path of cancer development and to direct treatment plans accordingly. In this direction, the cancer cell map

initiative (CCMI), developed recently by researchers at the University of California, San Francisco, and the University of California, San Diego, has been successful in charting how hundreds of genetic mutations involved in breast cancer and cancers of the head and neck affect the activity of certain proteins that ultimately lead to cancer progression. As there exists a vast amount of sequence data from many different cancer types, efforts are being made to extract mechanistic insight from the available information, and an integrated computational and experimental strategy will have to be employed to help place these alterations into the context of the higher order signaling mechanisms in cancer cells [10,107]. This is the defined goal of the CCMI and is likely to create a resource that will be used for cancer genome interpretation, allowing the identification of key complexes and pathways to be studied in greater mechanistic detail to gain insight into the biology underlying different types and stages of cancer [108]. Furthermore, researchers funded by the NIH have separately completed a detailed genomic analysis of data available through the TCGA program known as the 'PanCancer Atlas', providing an independent view of the oncogenic processes that contribute to the development of human cancer [109,110]. Analyzing over 11,000 tumors from the most prevalent forms of cancer, the Pan-Cancer Atlas has provided a most comprehensive, in-depth, and interconnected understanding of how, where, and why tumors arise in humans, focusing on how germline and somatic variants collaborate in cancer progression [111-112]. Considering the genes and pathways affecting different cancer types and individual tumors vary considerably, a complete understanding of these alterations become essential to identify vulnerabilities and discover precise therapeutic solutions [113]. Analysis of tumors profiled by TCGA to understand mutation patterns in selected signaling pathways reveals that most if not all, tumors possesses at least one driver alteration from these few pathways potentially targetable by drugs and some of them with multiple targetable alterations, providing opportunities for combination therapy. The synchronizing view on oncogenic processes based on PanCancer Atlas analyses tries to elucidate the possible consequences of genome alterations on the different signaling pathways involved with human cancers, also reflecting on their influence on tumor microenvironment and immune cell responses, to provide new insights into the development of new forms of targeted drugs and immunotherapies. Further, the stemness features extracted from transcriptomic and epigenetic data from TCGA tumors present novel biological and clinical insight for cancer stem cell targeted drug therapies [114]. Thus, a comprehensive analysis based on genomic studies of tumors essentially reveals the alterations in signaling pathways showing patterns of vulnerabilities and the means to identify prospective targets for the development of personalized treatments and new combination therapies. The challenge to identify the relevant genes and signaling molecules for different cancer types using cutting-edge technologies will remain an essential part of cancer research and is most likely to help vulnerable people undergo precise and efficient treatment for cancer with time. As a singular and unified point of reference, the Pan-Cancer Atlas can be taken as a vital resource to explore the influence of mutation on cancer cell signaling for the development of new treatments in the pursuit of precision oncology.

6. Integrating Artificial intelligence (AI) with Multi-Omics in Precision Oncology

Artificial intelligence: Artificial intelligence (AI) encompasses multiple technologies with the common aim of computationally simulating human intelligence to solve problems. Referred to as computer programming enabled to perform specific tasks, it is based on the principle that human intelligence can be defined in a way that a machine can easily mimic it and execute tasks from the simplest to even more complex ones successfully [115]. The term may be applied to any machine that shows traits associated with human understanding, such as learning and problem-solving. Artificial intelligence (AI) and related technologies have increasingly been prevalent in finance, security, and society, and are beginning to be applied to healthcare [116]. It has been widely applied in precision medicine based healthcare practices and finds use in medical oncology practice similarly. Many artificial intelligence algorithms have been developed and applied in cancer research in recent years. An exact understanding of the structure of a protein remains the first step to know all about its roles in cancer progression and therapeutic drugs are also designed using structural information of the target proteins where AI-based techniques can be used for the solutions. The development of next-generation sequencing (NGS), has led multi-omics data on cancer to become available to researchers providing them with opportunities to explore the genetic risk and reveal underlying cancer mechanisms to help early diagnosis, exact prognosis, and the discovery, design, and application of specific targeted drugs against cancer. Thus, taking the help of large datasets from multi-omics platforms, imaging techniques and biomarkers found and mined by artificial intelligence algorithms, oncologists can diagnose cancer early at its onset and help direct treatment options for individualized cancer therapy. The advances in AI now present an opportunity to perfect the methods of diagnosis and prognosis, and develop strategies for personalized treatment using large datasets, and future developments in AI technologies in this regard are most likely to help many more problems to be resolved swiftly. Artificial intelligence is the future of precision oncology for the prevention, detection, risk assessment, and treatment of cancer [117,118].

Machine learning: Machine learning (ML) is a branch of artificial intelligence that aims to develop computational systems with advanced analytical capabilities. It is concerned with the development of domain-specific programming algorithms with the ability to learn from data to solve a class of problems [119]. Therefore, the most common and purposeful application of traditional machine learning in healthcare seems to be in the area of precision medicine based and is most suited for the data-driven identification of cancer states and designing treatment options that is crucial to precision oncology (Fig. 2) [120].

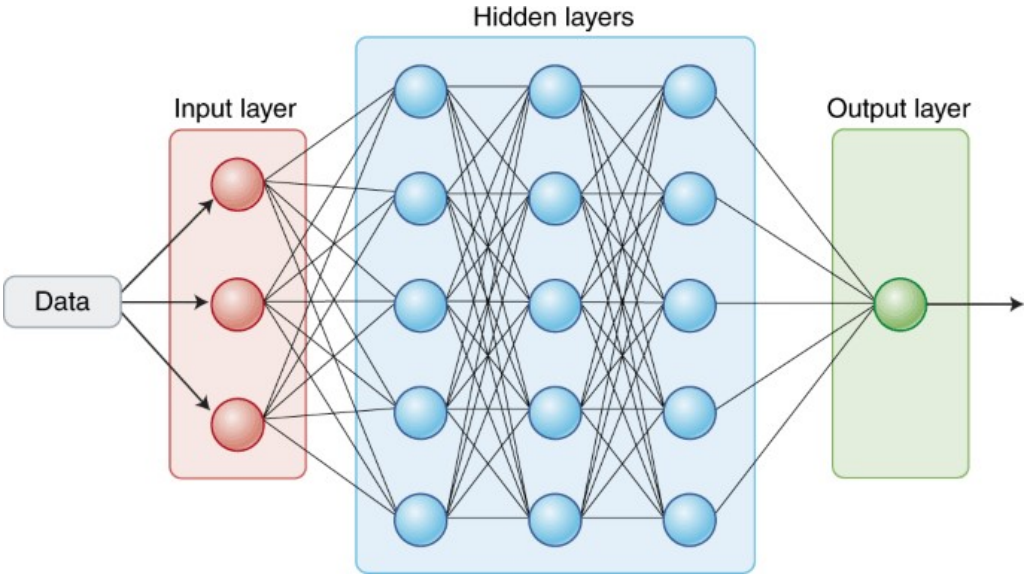

Figure 2. A deep neural network, simplified: the convergence of human and artificial intelligence. (Topol, E.J. [120])

Deep Learning: Deep learning (DL) is a sub-branch of ML that uses statistics and predictive modeling to extract patterns from large data sets to precisely predict a result. A variety of data have been appearing in modern biomedical research, including electronic health records, imaging, multiomics based reports, sensor data, etc., which are complex, heterogeneous, and poorly defined and need to be mined efficiently to bring correct results. To meet this end, DL uses a machine learning program called artificial neural networks modeled on the human brain that forms a diverse family of computational models consisting of many deep data processing layers for automated feature extraction and pattern recognition in large datasets to efficiently answer the problems. The human brain consists of neurons arranged together as a network of nerves efficiently processing several pieces of information received from many different sources to translate into a particular reflex action. In DL, the same concept of the network of neurons can be used on a machine learning platform to emulate human understanding to bring smart solutions. The neurons are created artificially on a computer system and the data processing layers work together to create an artificial neural network where he working of an artificial neuron should be taken as like that of a neuron present in the brain. Thus, DL is designed to use a complex set of algorithms, to enable it to process unstructured data such as documents, images, and text to find efficient results [121].

Efficacious drug development for cancer treatment is a major issue in cancer research and DL is coming of immense help to researchers in this direction. Changes in the genetic composition of tumors translate into structural changes in cellular subsystems that require to be integrated into drug design to predict therapy response and concurrently learn about the mechanism underlying a particular drug response. A proper understanding of the mechanism of drug action can lead researchers to understand the importance of the different signaling pathways including some new and uncommon pathways associated with tumors to help develop novel

drugs for therapeutic targeting of diverse forms of cancer. Drug combinations targeting multiple pathways are thought to be the answers to the incidences of drug resistance in cancer therapy where computational models could be used to find solutions. New advances in AI have enabled researchers to develop DL-based models to predict tumor cell response to synergistic drug combinations to be employed effectively in precision oncology [122]. A recent development in the DL system is AlphaFold which is being used to predict the structures of different proteins and the tool has already determined the structures of around 200 million proteins, from every known organism on the planet. Researchers continue to discover proteins that may be the key drivers of cancer and need a fuller understanding of the 3D shape, or structure, of these proteins to decide their exact functions in the cell [123,124]. This revolutionary new development in DL is going to be of great use in understanding the roles of suspected proteins in cancer development and in anticancer drug design. Thus,, DL finds multiple uses in healthcare like the prediction of treatment response, estimation of survival analysis, risk estimation, and treatment planning, and is becoming the main method in precision oncology [125].

Multiomics: High-throughput sequencing technologies, also known as next-generation sequencing (NGS), are a comprehensive term used to describe technologies that sequence DNA and RNA rapidly and cost-effectively. It has revolutionized the field of genetics and molecular biology and aided in the study of biological sciences as never before [126]. Technologies using NGS have been developed that measure some characteristics of a whole family of cellular molecules, such as genes, proteins, or metabolites, and have been named by appending the term "-omics. Multiomics refers to the approach where the data sets of different omics groups are combined during sample analysis to allow scientists to read the more complex and transient molecular changes that underpin the course of disease progression and response to treatment, and to select the right drug target for desired results [127]. It forms the basis of precision medicine in general and is at the core of the development of precision oncology, integrating it with artificial intelligence is the need of the hour and is likely to serve the purpose adequately with time [128,129].

7. Single-cell Technology to Unmask Tumor Heterogeneity

Tumor heterogeneity is a hallmark property of cancer and broadly refers to the differences between tumors of the same type in different patients, the differences in morphological and phenotypic profiles displayed by cancer cells within a single tumor, or the differences between a primary and a secondary tumor. The heterogeneous mixture of distinctly differentiated cancer cells includes connective tissue cells, immune cells, cancer stem cells, and vasculature, and these subpopulations of cells can be further distinguished by a variety of features impacting their phenotype, including genetic alterations. Heterogeneity within a single tumor, referred to as genetic intratumoral heterogeneity (ITH), has been documented across most cancers as an outcome of genome instability and clonal evolution [130,131]. Furthermore, researchers from different laboratories in the last decades have established tumor heterogeneity as a phenomenon

of critical importance in the history of individual neoplasms [132]. Recent investigations on drug resistance and tumor heterogeneity have converged to focus on the clonal organization of tumors as the underlying basis for drug resistance, thus indicating the need to fully understand the structure and dynamics of ITH to develop treatment strategies for the possible cure [133,134]. Thus, more precisely the cellular composition of a tumor is known, the mechanism underlying disease progression is understood, molecules and pathways involved in the process are identified, more specific therapeutic strategies could be devised to get the anticipated results. It is the stated goal of precision oncology-based cancer therapy and the emergence of single-cell technologies for biological analysis has become the crucial tool in this regard as they can carry out accurate single-cell measurements to provide a clear picture of tumor heterogeneity and reveal how structural changes in chromosomes can lead to the complex biological processes involved with carcinogenesis [135,136]. The rapid progress in the development of NGS in recent years has provided many valuable insights into cancer genomics, and NGS-based technologies for genomics, transcriptomics, and epigenomics have enabled laboratories to carry out related single-cell measurements efficiently. Single-cell genomics now facilitates the simultaneous measurement of thousands of genes in thousands of 'single' cells from a single specimen, allowing researchers to compare genomes of individual cells to determine the mutation profile of the cells to better understand the molecular consequences of the different variants present in the tumor microenvironment. The single-cell template strand sequencing (Strand-seq), a special single-cell sequencing technology now enables independent and efficient analysis of the two parental DNA strands resolving homologous chromosomes similar in shape and structure but not identical within single cells which is crucial to the identification of somatic SVs and unmask genomic rearrangements and tissue heterogeneity. Moreover, single-cell sequencing can also be combined with CRISPR knockout screening, a powerful tool of biological research that exploits the efficiency and flexibility of CRISPR–Cas9 genome editing to enable large-scale studies regarding how genetic modification can affect cell behavior or gain insights into a specific physiological condition required for better understanding of the underlying cellular processes for designing treatment options [137]. Combining both techniques to study gene functions with the concurrent use of single-cell resolution techniques, such as flow cytometry, microfluidics, manual cell picking, or micromanipulation, can have broad applications in cancer treatment, including identifying novel drug targets or studying unknown mechanisms of action of drugs [138].

The importance of epigenetic reprogramming in cancer is well understood, as evidenced by the fact that chromatin regulators are often mutated in the affected cells and the widespread epigenetic, changes throughout cancer genomes can be identified and linked to the activities of different known oncogenes and/or tumor suppressor genes. Abnormal epigenetic changes are usually influenced by aging, viruses, dietary factors, and environmental factors that may contribute to cancer progression. The interrelationship between genetic and epigenetic changes needs to be further examined for the discovery of screening markers to optimize pathways of diagnosis and prognosis and to develop strategies for individualized cancer treatment [139]. For example, DNA methylation is known to be associated with cell differentiation, aging, and diseases including cancer. A considerable amount of understanding exists regarding tissue-specific DNA methylation patterns, but it would reveal much less information about person-

specific DNA methylation causing cancer. Thus, the premise of epigenetic profiling holds great possibilities for deciphering the cellular states and characterizing phenotypic heterogeneity to pin specific mutations having profound effects on epigenetic pathways with therapeutic agents. The inclusion of epigenetics in clinical practice would require identifying epigenetic signatures that mediate distinct phenotypical changes of clinical relevance, such as mesenchymal transition, stems, dormancy, and quiescence or therapy resistance. Thus, single-cell sequencing technologies have been successful in leading scientists to better understand the cell types and features associated with the tumor yet, the spatial context of this development is essential to understand how cells organize and communicate across the tissue to fully unlock the repertoire of tumor heterogeneity. It will require a clear understanding of which cells are present, where they are situated in tissue, their biomarker expression patterns, and how they organize and interact to influence the tissue microenvironment [140,141]. It is an essential part of spatial biology and adds another dimension to single-cell analysis to unmask tumor heterogeneity. Spatial biology studies ordinarily try to combine whole-slide imaging (WSI), commonly referred to as 'virtual microscopy', at single-cell resolution to visualize and quantitate biomarker expression and reveal how cells interact and organize across the entire tissue landscape. This technique can support research for early biomarker discovery to late-stage translational research and therapy development. The latest development in this direction is spatial transcriptomics which has enabled researchers to visualize and quantify RNA down to the subcellular level and simultaneously compare gene expression in situ. It is a groundbreaking molecular profiling method that exploits the multi-omics technologies allowing us to measure all the gene activity in a tissue sample and assay the genetic information of single cells within their native tissue environment (Fig. 3) [142,143].

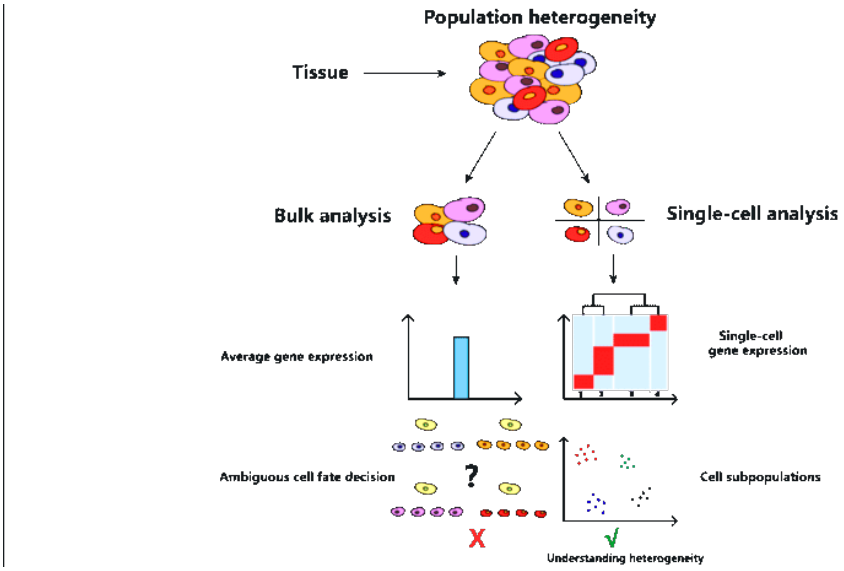

Figure. 3. Single Cell analysis reveals heterogeneity.

Traditional experiments on bulk samples mask the heterogeneity between individual cells. In order to understand the heterogeneity in complex tissue, analysis performed on single-cell resolution has been used to unveil cell subpopulations and their different gene expressions. (Ye, F., Huang, W. & Guo, G. [143])

The growing ability to demonstrate the role and function of distinct cell types present in the tissue paves the way for a new understanding of the tissue-specific cellular pathways and interactions that lead to cancer development. The precise molecular analysis of cancer cells based on single-cell technologies now aims to present an accurate picture of the most up-to-date development in the tumor microenvironment and detect changes in the genes and proteins responsible for alterations in cellular processes to better understand the prognosis and pathways of cancer progression. New advances in multi-omics techniques powered by AI have now enabled researchers to integrate genomic, transcriptomic, epigenomic, and other related data to reveal the most accurate information on the activity state of individual genes to help detect novel cancer drivers and genetic vulnerabilities for prevention and cure [144,145]. The emerging field of single-cell technology thus provides an unprecedented insight into the complex genetic and epigenetic heterogeneity within individual tumors for advanced precision oncology-based treatment and is most likely to streamline the research directions in the future.

8. Precision Oncology and Targeted Drug Therapy of Cancer

Targeted drug therapy is a new form of cancer treatment that targets specific genes and proteins of cancer-related signaling pathways and molecules in the tumor microenvironment that contribute to cancer development. This contrasts with the single-target approach employed in chemotherapy to primarily target and kill actively dividing cancer cells with serious side effects and can be seen as the natural outcome of decades of studies on cell reprogramming in different cancers. Some noticeable breakthroughs have come in certain cancers as the understanding of the signaling pathways underlying cancer development has led to the development of specific targeted drugs that have certainly revolutionized the treatment of the disease [146.147]. This form of cancer therapy can be optimized by taking advantage of genomic profiling of sample from a patient to look for the mutations to learn about the signaling pathways that the mutations disrupt lading to the disease toward a possible cure

Therapeutic agents that can mitigate the acquired capabilities necessary for tumor growth and cancer progression are being developed for clinical use in treating different cancers types. These drugs are being developed in clinical trials to target each of the emerging neoplastic characteristics and enabling hallmarks capabilities towards an effective cancer therapy. The listed drugs are just illustrative examples; there is a deep pipeline of investigational drugs in development to target different signaling molecules and intermediates involved with most of these hallmarks.The anticancer drugs employed in targeted therapy are designed to target selected molecules directly involved with cancer cell signaling or those in the tumor microenvironment, essentially required for tumor growth and cancer manifestation [148,149].

They can be broadly classified as monoclonal antibodies (mAbs) or small-molecule drugs. The therapeutic mAbs are modified monoclonal antibodies, also called anti-CTLA4 monoclonal antibodies, that target antigens found on the cell surface of the cytotoxic T-lymphocytes, whole the small molecule drugs can directly approach the cell membrane to interact with targets inside the cell and are usually designed to inhibit the enzymatic activity of target proteins such as the proteasome complex, tyrosine kinases or cyclin-dependent kinases. A type of targeted therapy, called tumor agnostic therapy uses drugs and other substances to target certain genetic changes or markers as cancer-specific features to treat the ailment without requiring a focus on the cancer type or where cancer may have started in the body. The use of monoclonal antibodies in targeted therapy is being explored, as they may be exploited successfully for potentiating the natural immune system, addressing the concern related to changes in the immunogenicity of cancer cells. The goal of immunotherapy remains to activate the individual's own immune system against the evolving tumors to successfully target the transformed cells with high selectivity, low toxicity, and appropriate responses. Several immune checkpoint proteins capable of binding with partner proteins to help cancer cells escape immune responses, are activated in tumors limiting immune cell response like T-cell infiltration and effector functions in cancer. The mAbs may be designed to coat the cancer cells to be recognized and destroyed by the immune cell, block the activity of certain abnormal proteins in the affected cell, or inhibit the immune checkpoint proteins to limit immune evasion in cancer development [150,151]. Targeted drug therapy and monoclonal antibody-based therapy need to be seen as potent means of cancer treatment and are becoming increasingly important in cancer therapy [152,153].

Targeting DNA damage response (DDR) signaling is an emerging field of selective targeted cancer therapy that exploits the options of targeting cancer cells with exceeding deficiencies in homologous recombination (HR) signaling such as BRCA-mutated cancers. Poly(ADP-ribose) polymerase (PARP) and Inhibitors of poly(ADP-ribose)glycohydrolase (PARG) are the most important DNA repair enzymes that work synergistically in many different DDR pathways, including base excision repair, non-homologous end joining, nucleotide excision repair, homologous recombination (HR), maintenance of replication fork stability and nucleosome remodeling. The enzymes are essentially involved inthe process of single-strand break (SSB) repair whose failure will lead to the conversion of SSB into double-strand breaks(DSB) requiring repair by HR toprevent death. Such lethal genetic interactions, known as synthetic lethality, may be exploited to develop anticancer therapeutics and the enzymes of DDR signaling fit the needs adequately. Overexpressed of these proteins have been witnessed in different cancer types such as pancreatic, prostate, breast, ovarian, and oral cancers, allowing the options for inhibiting PARP activity as an effective therapeutic strategy. PARP and PARG inhibitors have shown improved results in different forms of tumors, and are under investigation for being used in combination therapy. [154,155]. However, a major concern in cancer therapeutics remains proper drug delivery to the affected cells and tissue for anticipated outcomes. Conventional chemotherapeutics may possess some serious side effects due to nonspecific targeting or inability to enter the core of the tumors, resulting in impaired treatment and a low survival rate. Researchers have been trying to address the issue with more specific methods of drug delivery including the use of nanotechnology in cancer therapeutics. Nanoparticles can be programmed to recognize cancerous cells for selective and accurate drug

delivery with increased drug localization, solubility, and cellular uptake avoiding encounters with healthy cells, they will serve the needs better if the treatment is tailored to the requirements of the vulnerable individuals [156,157]. In this direction, antibody drug conjugates (ADC) is a fast expanding therapeutic strategy designed to selectively delivery drugs to cancer cells. ADCs are monoclonal antibodies linked with small molecule cytotoxic drugs through a chemical linker capable to approach the cancer cells and attach to the specific tumor antigens on the cell surface for direct drug delivery sparing healthy cells in the surroundings. They are designed to exploit the features of antigen antibody specificity for efficient drug delivery and being considered as the magic bullets in targeted cancer treatment. Recent advances in cancer genomics and single-cell technologies have certainly made targeted therapy the accepted form of cancer treatment, and yet a huge amount of investment will be needed for future research, drug discovery, and diagnostics to fully unlock its potential and for their application in the management of cancer incidences in the time to come (Fig. 4).

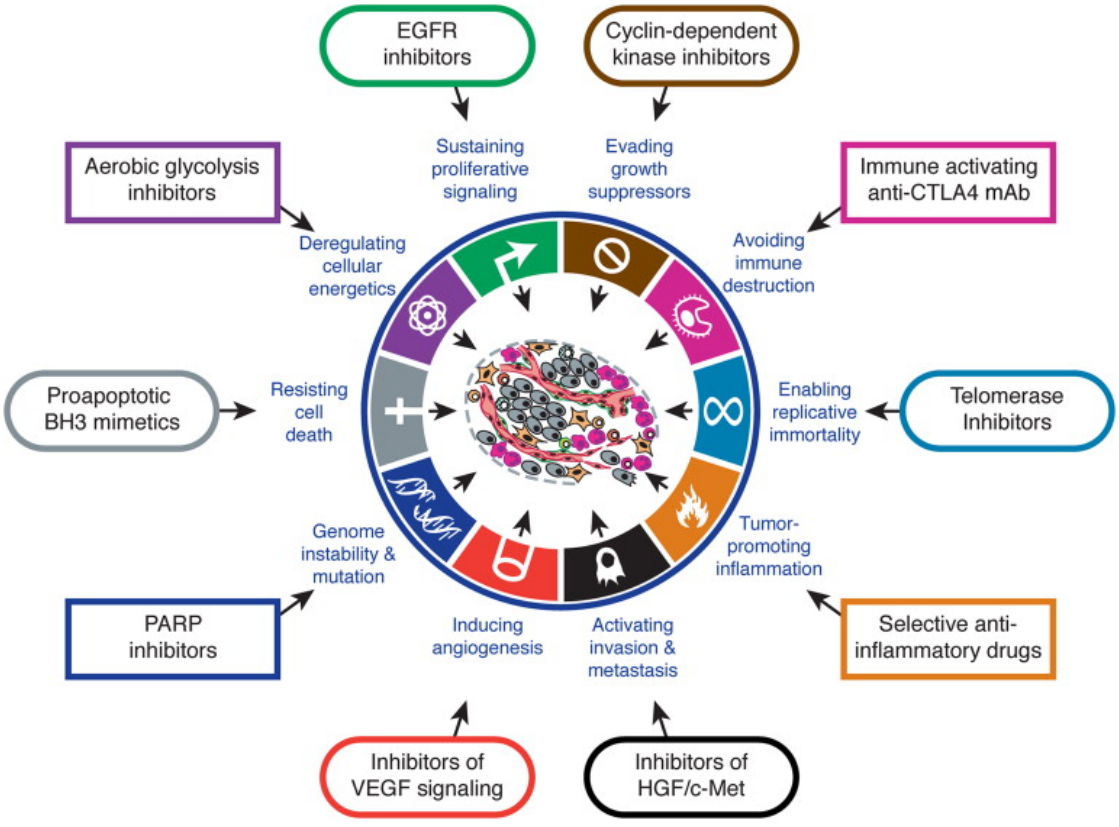

Figure 4. Therapeutic Targeting of the Hallmarks of Cancer

Therapeutic agents that can mitigate the acquired capabilities necessary for tumor growth and cancer progression are being developed for clinical use in treating different cancers types. These

drugs are being developed in clinical trials to target each of the emerging neoplastic characteristics and enabling hallmarks capabilities towards an effective cancer therapy. The listed drugs are just illustrative examples; there is a deep pipeline of investigational drugs in development to target different signaling molecules that lead to the hallmark capabilities. (Hanahan and Wienberg [57].)

The field of precision oncology appearing as the new branch of cancer research is essentially directed at strategizing targeted drug therapy by exploiting the peculiarities of the cancer genomes of the individuals and/or a court of patients for desired results. It is dedicated to studying the genetic profile of cancer cells to gain a thorough understanding of the signaling pathways and related molecular events during tumor growth and metastases and of the mechanisms associated with drug resistance in cancer therapy for a possible cure [158,159]. Let us not forget that the socioeconomic burden of cancer remains high as the treatment options for most common cancers have been limited thus far and is an indication for a renewed approach to expedited drug development to bring effective anticancer agents from bench to bedside in a cost-effective manner. The lack of understanding of the genetic heterogeneity of individual cancers has traditionally been limiting the search for efficacious agents for cancer treatment and missing a wide range of possibly suitable agents from other disease areas. The use of molecular characterization of different cancer types through cancer genomics can help resolve drug-related issues to a reasonable extent by repurposing the use of certain existing drugs as anticancer agents for a wide range of applications, and it will remain at the forefront of precision oncology [160,161]. Furthermore, the move from tissue or cancer-specific treatments to genomic or target-based treatments entails the reuse of anticancer drugs prescribed for one type of cancer to treat other cancer types with time. It is envisaged that with the ever-greater understanding of cellular signaling mechanisms and genetic alterations in carcinogenesis in the age of cancer genomics considerable progress in cancer treatment will be realized sooner ONLY. Considering that academia, industries, and civil society will be working in tandem to cater to the needs of the system, it is hoped that a wide range of people with cancer will benefit from this new development in cancer research in the future to benefit the society as a whole [162,163].

9. Conclusion

Precision oncology-based cancer therapeutics propose to develop treatments that target the specific molecular characteristics of an individual's tumor instead of targeting the common features of certain cancer for a cure. Considering the way, a thorough understanding of the genetic composition and heterogeneity of the individual's tumor is now becoming possible through single-cell technologies, it is poised to help individuals get the right treatment at the right time rather successfully without requiring them to go through more generalized treatment that would prove mot very effective in the end. Precision medicine approaches to treat inherited diseases have been in use for directly targeting associated pathways and proteins, and such methods can be employed in the treatment of inherited cancers as well. Furthermore, cancer research has traditionally been focused on common cancers for obvious reasons leaving therapeutic options for less frequent tumor types largely limited and such anomalies are likely to

be addressed with the new development successfully. In this way, precision oncology emerging as a new field of cancer research focusing on the identification of specific mutations in the cancer genome to selectively target the most specific pathways involved with disease progression is very likely to bring in the right treatment for the disease. It appears to be the natural outcome of the cancer genome project, and, considering the level of support coming from multi-omics platforms, it is destined to satisfy the intended purpose of the initiative satisfactorily. The success of this form of treatment is sure to further strengthen our belief in the possibility of a proper cure for cancer and needs to be accessible to a larger number of people with cancer toward the realization of goals with time.

Declarations:

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Data Availability: The datasets analyzed during the current study are available in the repository named in the manuscript

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Supplementary File 1: Ongoing/ Cancer Accelerated Approvals (https://www.fda.gov/drugs/resources-information-approved-drugs/ongoing-cancer-accelerated-approvals)

Supplementary File 2: Oncology (Cancer) _ Hematologic Malignancies Approval Notifications _ FDA (https://www.fda.gov/drugs/resources-information-approved-drugs/oncology-cancer-hematologic-malignancies-approval-notifications)