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

Manish Kumar[1,1]

[1]School of Bio Sciences & Technology, Vellore Institute of Technology, Vellore - 632014, Tamil Nadu, India

December 14, 2023

Abstract

Cancer is a complex disease having a number of composite problems to be considered including cancer immune evasion, therapy resistance, and recurrence for a cure. Fundamentally, it remains a genetic disease as diverse aspects of the complexity of tumor growth and cancer development relate to its genetic machinery and require addressing the problems at the level of genome and epigenome. Importantly, patients with the same cancer types respond differently to cancer therapies indicating the need for patient-specific treatment options. Precision oncology is a form of cancer therapy that focuses on the genetic profiling of tumors to identify molecular alterations involved in cancer development for custom-tailored personalized treatment of the deadly disease. This article aims to briefly explain the foundations and frontiers of precision oncology in the context of ongoing technological advances in this regard to assess its scope and importance in the realization of a proper cure for cancer.

Posted on 14 Dec 2023 — CC-BY-NC-SA 4 — https://doi.org/10.22541/au.167759758.86521674/v13 — This is a preprint and has not been peer-reviewed. Data may be preliminary.

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

---

Manish Kumar

School of Bio Sciences & Technology

Vellore Institute of Technology, Vellore, Tamil Nadu, India

Emails: kmanish125@yahoo.com, kmanish.bt125@gmail.com

ORCID: https://orcid.org/0000-0002-6021-7063

CORRESPONDENCE

1.

C/O. Sri M. Narayan Swami

7/1A, 1st Street, Bhavani Nagar

Katpadi P.O. Dharapadavedu,

Vellore- 632007, Tamil Nadu, India

2.

ME-010-0017, Dhruvneeti Colony

Near Samarpan Hospital, Rajneeti Road

Madhopur, P.0. Basudeopur

Munger- 811202, Bihar, India

Abstract: Cancer is a complex disease having a number of composite problems to be considered including cancer immune evasion, therapy resistance, and recurrence for a cure. Fundamentally, it remains a genetic disease as diverse aspects of the complexity of tumor growth and cancer development relate to its genetic machinery and require addressing the problems at the level of genome and epigenome. Importantly, patients with the same cancer types respond differently to cancer therapies indicating the need for patient-specific treatment options. Precision oncology is a form of cancer therapy that focuses on the genetic profiling of tumors to identify molecular alterations involved in cancer development for custom-tailored personalized treatment of the deadly disease. This article aims to briefly explain the foundations and frontiers of precision oncology in the context of ongoing technological advances in this regard to assess its scope and importance in the realization of a proper cure for cancer.

Keywords: Gene Mutation; Cancer Genomics; p53; K-Ras; C-Myc; Bcl-2, Cancer Stem Cells; Targeted Therapy; Immunotherapy, Precision Medicine.

1. Introduction

Cancer is a devastating disease causing one in six deaths globally with a huge physical, psychological, and economic impact on people affected by the disease. It continues to be the second most common cause of hospital deaths after heart disease, most of which can be prevented by an early diagnosis and improving prevention and treatment strategies for the disease. It requires an efficient diagnosis of cancer, the development of efficacious treatment options, and a better understanding of the socioeconomic factors that affect cancer incidence, prevalence, and related deaths across the globe [1,2]. More than 100 cancer types with sub-types have been determined based on location, cell of origin, and genetic variations that influence cancer development 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 also develop frequently in hematopoietic tissues such as leukemia and lymphomaand in the nervous tissues, e.g., gliomas, and neuroblastomas. They are among the most commoncancer types taking a high toll in terms of lives and property throughout the world [3,4]. Thus, considering the vast number of cancer incidences worldwide, a formal initiative towards fightingthe menace of cancer was needed which first appeared in the United States as the National Cancer Act of 1971 signed by President Richard Nixon, for promoting cancer research and application of the outcomes for minimizing cancer incidences and mortality rates associated withthe disease. The act was euphemistically described as the "War on Cancer", and 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 the treatment, cure, and eradication of cancer [5]. A similar approach was adopted by most other developed and developing nations in the following years to combat the deadly disease which has succeeded in satisfying the purpose involved to a good extent since then despite the fact, as feared and as evidence suggests, that demographic factors played a role in cancer development [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 the rapid advances realized in clinical oncology over the years. [8.9]. However, the fight against cancer is far from over as an estimation by the WHO in 2018 revealed that cancer incidence would be doubled to

approximately 37 million new cases by 2040 with no confirmed remedy for most cancer types in the sight [10,11]. While researchers continue the endeavors to identify the exact causes of different 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 therapy available for cancer for quite some time such as chemotherapy, immunotherapy, hormonal therapy, targeted drug therapy, radiation therapy, surgery, stem cell transplant, etc. One can receive a single type of treatment or a combination of therapies, but whatever the treatment regimen, it must bring the much-needed cure that remains largely elusive till now [12].

Rigorous cancer research in the past few decades supported by advances in cell and molecularbiology has led scientists to clearly understand there are genetic changes associated with cancer incidences that cause the disease to grow and spread to other parts of the body. Cancer is initiated as the result of uncontrolled cell division and proliferation leading to tumor formation which culminates in metastasis that involves the dissemination of tumor cells to new sites in the body forming secondary tumors, and is responsible for about 90% of cancer-related deaths in reality. Cell proliferation requires a balanced rate of cell growth and division to maintain the increase in cell numbers for growth and development, maintenance of tissue homoeostasis and wound healing. The fundamental abnormality leading to cancer development is unwanted cell proliferation due to an absence of balance between cell divisions and cell loss through cell death and differentiation. The division relies on cell cycle regulation that generally involves extracellular growth-regulatory signals as well as internal signaling proteins monitoring the genetic integrity of the cell to ascertain that cellular developments go well in time. It 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 in the transformed cells of the tumor and other cellular activities accompanying cancer progression such as angiogenesis, invasion and metastasis are mainly guided by changes in the concerned genes, and the factors that cause these genetic changes often tend to provoke cancerous development [13,14]. Every single gene in the body is likely to have received deleterious changes in its DNA sequence, i.e., mutations on a number of occasions in the cell's lifetime while the repair mechanism in place would restrict the noticeable changes. In this way, the generation of cancer must be conclusively linked to the sustained gene mutations caused by some external agents called mutagens that often lead to the appearance of different somatic variants or certain changes that might have been inherited in the body. Importantly, a single mutation will not be enough to transform a normal cell into a cancer cell as it would require a number of changes to accumulate in the cells in the course of time for cancerous development to take place. For example, 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 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 ordinarily be required for cancer manifestation to take place and so it must 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. 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 [16]. It is observed because of some physical modificationsin chromatin structure capable of influencing the pattern of gene expression often led by DNA methylation, histone modifications, and miRNA-based alterations inside the cell. Epigenetic regulations of DNA and RNA usually control how genes are turned on or off, and so play important roles in maintaining normal cell behavior whose deregulation causes alterations in gene expression patterns to potentially influence tumorigenesis. The changes are frequently accompanied 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. Although epigenetic changes will not alter the sequence of DNA, 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 may is not the whole regarding 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. Thus, the genome and the epigenome could regulate the progression of cancer through mutations. Interferences between the two are therefore anticipated and can be exploited to provide new possibilities for cancer treatment [17].

Cancer in general remains a multi-step process triggered by mutations leading to the activation of specific oncogenic pathways with the concurrent inactivation of tumor suppressor genes that act as sentinels to control unwanted cell growth and proliferation. Scientists have been trying to analyze the totality of cancer-causing gene mutations regarded as the “mutational landscape’, of different types of cancer types and to target them effectively for cancer cure. Most of these biochemical processes are conserved in model organisms such as the free-living transparent nematode Caenorhabditis elegans and the fruit fly Drosophila melanogaster alongsidemice and other large animal models, and are widely used due to the ease of their genetic manipulation to study the complex biology of cancer. The somatic cell mutations, called 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 [18]. 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 are sure to 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 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 reveal 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. Cancer whole-genome sequencing (WGS) remains the most comprehensive method for identifying variants in non-coding regions as targeted approaches like exome sequencing (WES) may miss certain variants residing outside the coding regions [19]. Pieces of evidence suggest oncogenesis typically involves interplay between germline and somatic variants and different modes of action of non-coding variants could further potentiate these developments. Thus, a systematic approach to unraveling the roles of the non-coding genome in cancer progression should help improve cancer diagnosis and therapy [20].

2. Cancer Genomics and the Emergence of Precision Oncology

As a matter of fact, changes in vulnerable genes involved in cell growth, proliferation, death, or differentiation appear to be essential for all the changes in cell behaviors and remain the most fundamental feature of all cancers, so cancer has to be seen as a genetic disease to be treated accordingly for better outcomes. Over the years, technological advances in the field of molecular biology have been exploited to unravel genomic changes to fully understand the pathogenesis of human cancer. The range of cancer-causing mutations is known to be huge, and 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. Moreover, it has long been observed that every patient responds differently to particular treatments despite having the same type and stage of cancer. These observations have been compelling and led researchers to adopt a precision medicine approach to cancer therapy necessitating the study of genetic features of vulnerable individuals for a patient-specific treatment regimen towards the most effective treatment of cancer [21]. 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. 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 field of cancer research that takes into account the genetic specificities of the individuals for a possible cure. [22]. The term, precision oncology has been coined for the specific clinical oncology practice that relies upon genomic profiling of individual tumors for a complete molecular characterization of the transformed cells and tissues to identify and target specific molecular alterations for efficient cancer therapy [23]. Thus, precision oncology intends to bring a perfectly planned cancer therapy by designing a custom-tailored treatment regimen for vulnerable individuals by identifying their unique needs for the best possible results. The effectiveness of precision oncology has been tested through progressive clinical trials on different tumor types and recent precision oncology trials that include the NCI-MATCH (Molecular Analysis for Therapy Choice) or the NCI-MPACT (Molecular Profiling-based Assignment of Cancer Therapy) have helped shift the focus from cancer treatment based on type and origin to targeting cancer-specific genetic mutations for cure [24]. The discovery of imatinib for the treatment of chronic myeloid leukemia virtually marks the beginning of precision oncology management. Thus, the good use of precision

oncology in clinics began about 25 years ago, but has significantly improved the effectiveness of cancer treatment and is about to enter the mainstream of clinical practice. [25].

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, prognosis, and treatment which have proven to be immensely helpful in advancing precision oncology [26]. There are many potential biomarkers in cancer. and many prognostic biomarkers are therapeutic targets for cancer treatment.

3. Molecular Basis of Cellular Reprogramming and Cancer Therapy

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 cancer cells, and no gene change is thought to be common to all cancers [27]. 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, observations 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 involve 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 in promoting 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 andis often involved in promoting invasion and metastasis Cancer cells can develop novel mechanisms for evading apoptosis and autophagy and new discoveries direct toward the possibleinterrelationship 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. Furthermore, cancer cells maintaining constant proliferative capacity may be guided by their transformation into everlasting non-senescent cells. In this regard, telomeres are the specific repeating DNA structures found at the ends of the chromosome of the cell, which protect the genome against unnecessary nucleolytic degradation, recombination, repair, and interchromosomal interactions. Telomeres are maintained by telomerase which adds nucleotides to telomeres to keep them from getting shorter. Germ cells typically express high levels of telomerase to maintain telomere length. In somatic cells, telomere length usually decreases with the lapse of time, leading cells to undergo senescence with age. Loss of cells in this way generally acts as a barrier to tumor growth which the transformed cells escape as they maintaintheir telomeres despite repeated cell divisions because these cells are able to express a lot of active telomerase. Telomerase has become a potential target in cancer therapeutics as they are over-expressed in transformed cancer cells and cancer stem cells in diverse forms of malignancies. Telomere maintenance mechanisms (TMM) are used by cancer cells through telomerase activation and sometimes by alternate means called alternative lengthening of telomeres (ALT).to avoid apoptosis. Anti-telomerase therapeutics have been developed to selectively target cancer cells to induce cell death by apoptosis without affecting normal cells [28].

An important feature of cancer is that the population of cells that make up cancer is profoundly heterogeneous at the genetic, and epigenetic levels. Tumors usually represent a heterogeneous mass of distinctly differentiated cells that include 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 that generally involve genetic alterations. Tumors develop this feature mainly because the cancer genome is unstable due to accumulating numbers of cancer-causing gene mutations. Genomic instability further promotes genetic diversity by providing the raw material for the generation of tumor heterogeneity [29]. There are transposable elements (TEs) present in the cells called 'jumping genes', the repetitive sequences of DNA that move from place to place in the genome by different means. and represent almost half of the human genome. They represent a powerful means of genetic modification and have played an important role in the evolution of genomes. TEs are typically regulated since the early stage of development and throughout the lifespan by epigenetic mechanisms such as DNA methylation and histone modifications and are crucial for maintaining genomic stability through the regulation of transcriptomic and proteomic profiles of the cell. Dysregulation of TEs has been implicated in different types of human cancers, with the possibility of chromosomal aberrations, oncogenic activation, transcriptional dysregulation, and non-coding RNA aberrations as potential mechanisms underlying the development of cancer. Further, there are fragile points in every genome where the DNA is more likely to be mutated when the genome is replicated. These breakage points have frequently been linked to genetic and heritable disorders like cancer. Moreover, there can be mutations present in certain genes, known as mutator mutations, that further increase the inherent rate of genomic changes, resulting in even greater genetic instability that leads to the accumulation of multiple oncogenic mutations within a cellular lineage. Not all such changes are "malignant", but the rate of such development could translate into cancer manifestation at different stages in a lifetime. Mutator mutations and genetic instability are generalized concepts in cancer genetics, referred to as mutator hypothesis, that relates to those few mutations that lead to an enhanced rate of the gene mutations leading to chromosomal instability, microsatellite instability, and deregulation of 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 relevant measures for prevention and cure. 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. Researchers have begun examining the genomic data of vulnerable individualsto allow clinicians to embark on the path of personalized radiation therapy.

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 bythe 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 [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].

4. Targeting Genetic Alterations in Medical Oncology

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 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. 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 the 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 findings have revealed many crucial genes and proteins associated with the pathways of cancer reprogramming which could be taken as attractive targets for precise cancer treatments. These molecules are thought to participate in crucial cellular events in different ways eventually leading to uncontrolled cell growth and proliferation responsible for tumor growth in our bodies. A few common alterations that are frequently implicated in cancer progression with profound effects are detailed below.

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 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 to 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 of maintaining 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 [43].

A series of growth factors and their receptors are involved in cancer development and metastasis. Receptor tyrosine kinases (RTKs) are a class of receptors for many polypeptide growth factors, cytokines, and hormones that can play vital roles in cancer development. RTKs are cell surface receptors with specialized structural and biological features capable of dimerizing with other adjacent RTKs leading to rapidly phosphorylating tyrosine residues on target molecules to initiate several downstream biochemical cascades in the affected cells. RTKs like Fibroblast growth factor receptor (FGFR), Epidermal growth factor receptor (EGFR), Platelet-derived growth factor receptor (PDGFR), and Vascular endothelial growth factor receptor (VEGFR) control vital functions such as cell growth, proliferation, differentiation, apoptosis, inflammation, and stress responses. These cellular processes can be critical for reciprocal interactions between tumors and stromal cells and play a central role in the control of

tumor formation, angiogenesis, and metastasis [44]. The multifaceted role of RTKs makes them suitable candidates for selective targeting in cancer therapy but their involvement with alternate pathway activation often presents serious challenges to anti-RTK therapy.

The trimeric GTP-binding protein (G protein) mediated signaling is critical to many cellular processes and minor defects in the related pathways 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, which remain attached to the cytoplasmic face of the plasma membrane, 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 specifically associate 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 [45]. 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). 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 number 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 [47]. 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.

The nuclear factor erythroid 2 (NFE2)-related factor 2 (Nrf2) belongs to CNC (cap‘n’collar) family proteins, a group of basic leucine zipper (bZip) transcription factors encoded by basic leucine zipper (bZIP) genes, which serves as the master regulator of the cellular antioxidant response. Recent studies have revealed many new roles for Nrf2 in the regulation of essential cellular processes through 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 chemopreventive 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 [48].

The insulin-like growth factor receptor (IGF-1R), is an RTK that binds IGF1 with a high affinity and is an important factor in the growth, differentiation, and survival of cells in health and disease. IGF-1R plays an important role in the anchorage-independent growth of cells, which may enable cancer cells to survive and grow in the absence of anchorage to the extracellular matrix (ECM) and the neighboring cells. High gene expression level for IGF-1 and IGF-1R have been associated with the upregulation of pathways supporting cell growth and survival, cell cycle progression, angiogenesis, and metastatic activities during cancer development, and is considered essential in many cancer types [49].

B-cell lymphoma-2 (Bcl-2) oncoprotein is primarily a cell death regulatory protein that controls whether a cell lives or dies by apoptosis. 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 crucial roles in oncogenesis. An aberrant expression of the BCL2 gene may keep cancer cells from dying and is frequently implicated in prolonged cell survival and therapy resistance in human cancer. The Bcl-2 family proteins form subgroups, one of which may inhibit cell death and prolong cell survival by 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 upregulation of pro-survival Bcl-2 proteins. The important role played by Bcl-2 family proteins in cancer development renders them potential targets for the 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 BH3-mimetic drugs may prove to be novel agents for cancer therapy.

5. Signaling Pathway Deregulation and Prospective Targets for Cancer Therapeutics

The root cause underlying cancer progression is genetic and 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 signaling network as the foremost system of communication between cells and the surroundings that

involve a variety of chemical and mechanical signals to regulate different signaling pathways comes into consideration here as all the essentials of cellular behaviors like cell growth and proliferation, cell polarity, cell metabolism, differentiation, survival, and migration can be seen guided by the components of these pathways working in a collaborative manner in the cell. The signaling pathways together maintain an internal circuitry inside cells guided by external stimuli enabling them to 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]. Almost all gene modifications can be related to one or more of these signaling pathways that are deregulated in the affected cells to acquire hallmark properties of cancer. Cancer cell signaling displays altered expressions of the components of the signaling network that include many secreted protein receptors, growth factors, protein kinases, phosphatases, different cytoplasmic proteins, and transcription factors leading individual cells to respond to the changes with appropriate physiological behaviors. Cell division is mainly regulated by a group of extracellular growth factors that signal resting cells to divide by exploiting the intrinsic regulatory process of the cell. 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 camefrom 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. Theoncogenic 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. Many of these mutations have been directly linked to the growth factors and their receptor proteins involved with tumor growth, angiogenesis, invasion, and metastases [55,56].

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 EGFR, FGFR, IGFR, VEGFR, 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 process evidently presents the option for crosstalk between components of different signaling pathways at different stages of the cellular process. A molecule participating in crosstalk can affect the activation of alternate signaling pathways, and receptors can also have an altered ability to bind to the ligands which can 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 the estrogen receptor (ER), EGFR/HER, or IGFR, but in many cases, molecules and intermediates of multiple signaling pathways can be interactively involved in the process. In this way, the many signaling molecules affecting cancer cells together could beconsidered to create elaborate

integrated circuits within the cell, derived from the usual signaling circuits that operate in normal cells. The transformed intracellular circuit could be divided into distinct subcircuits specialized in specific cellular activities to promote hallmark features of cancer [57] (Fig. 1). Signal transduction leading to tumor growth, cancer cell migration, metastasis, and drug resistance are often complex processes, as cancer cells typically develop abnormalities in multiple signaling pathways or rely on crosstalk between different pathways and some redundant pathways for maintenance of growth and survival.

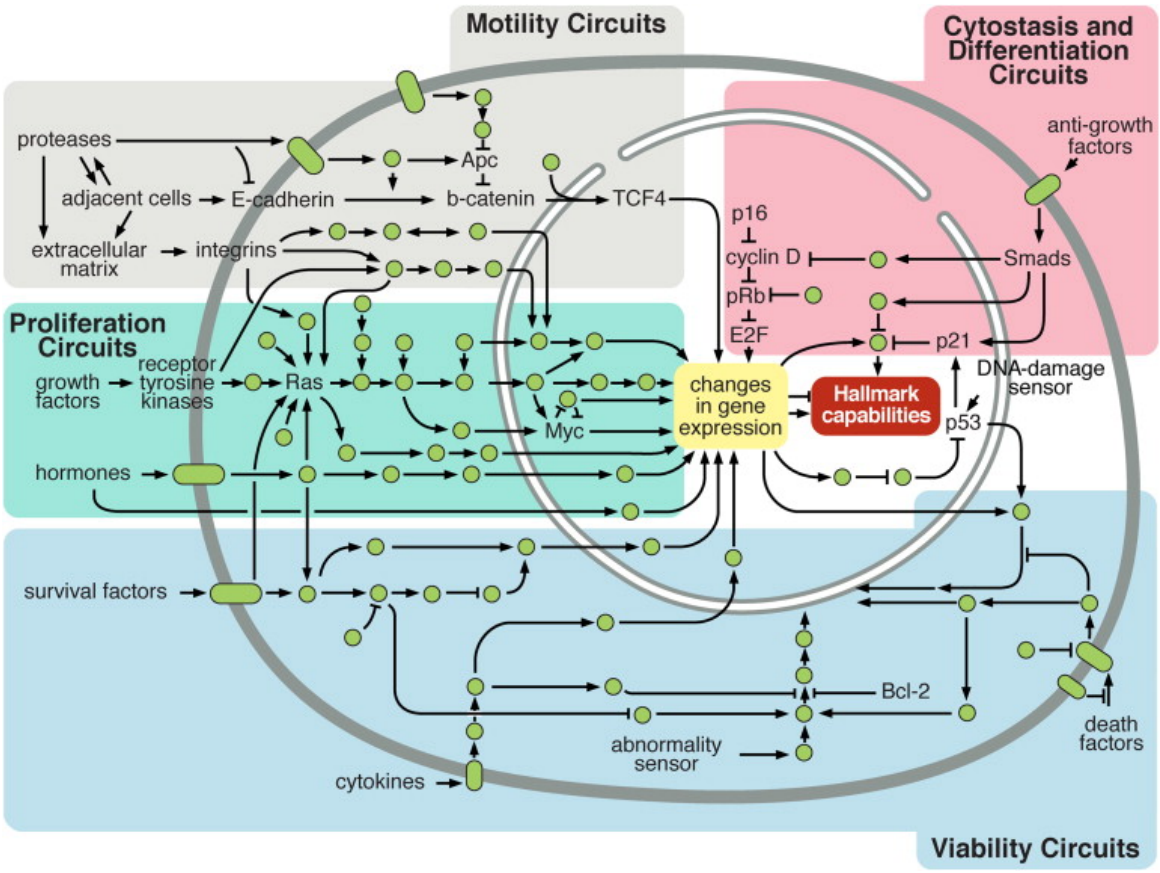

Figure 1. Intracellular Signaling Networks Regulate the Operations of the Cancer Cell.
An elaborate integrated circuit operates within normal cells and is reprogrammed to regulate hallmark capabilities within cancer cells. Separate sub-circuits, depicted here in differently colored fields, are specialized to orchestrate the various capabilities. At one level, this depiction is simplistic, as there is considerable crosstalk between such sub-circuits. 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]. With permission from Elsevier)

As cancer progression involves alterations in signaling pathways due to mutations in the relevant genes, it is satisfying and mechanistically well-founded that a therapeutic intervention taking into account this biology of the affected cells can pave the way for a very effective cancer treatment [58,59]. Further, it has been established in clinical practice that targeting a single intermediateor pathway brings considerable results toward recovery, possibly because it impedes the synergistic signaling process of disease progression. Yet, the constitutive activation of a molecular event that contributes to cancer development can be sustained by different

mechanisms, and strategies to inhibit multiple targets or redundant pathways simultaneously with molecular-targeted agents could prove to be an even more effective way to treat cancer and overcome resistance in cancer therapy [60]. It has indeed been tried with anticipated outcomes in some forms of cancer, indicating the need for more research in that direction. The representative signaling pathways involved in cancer cell reprogramming and the scope for therapeutic targeting of the signaling molecules and intermediates for efficient cancer treatment 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 proteins. It may act as a molecular switch that controls 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 the evolutionarily conserved signaling system that is activated by MEK. It is activated by Raf which, in turn, is targeted 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 are ongoing for the efficacious treatment of the disease [63].

PI3K/Akt/mTOR signaling pathway: This pathway can be 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 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 by participating in multiple signaling pathways inside the cell and is actively involved in cell growth, proliferation, autophagy, and apoptosis. The canonical pathway of mTOR activation depends on signaling through PI3K/Akt, though alternative non-Akt dependent activation through the MAPK pathway is now so well recognized. 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 a variety cell behaviors. Persistent mutational activation of the PI3K/Akt/mTOR

pathway in the absence of different stimuli has been frequently observed in many cancers. Several mTOR inhibitors have also been developed to treat cancer, and some are being evaluated in clinical trials for approval [64,65]. In addition, Phosphatase and tensin homolog (PTEN)), a potent tumor suppressor, is a crucial component of this pathway that can work independently as a phosphatase against phospholipids and proteins. Its primary target is PIP3, the direct product of PI3K which is crucially involved in the signaling process. Mutational deregulations of the PTEN/ PI3K network have been associated with many cancer types including familial cancers. It is a potential means of targeting PI3 K-mediated signaling in cancer therapeutics [66]. Adaptive resistance to the pathway inhibitors is common, and combination therapy, if well tolerated, may produce favorable anticancer results [67].

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 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 [68,69]. 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 [70]. 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 [71,72].

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 malignancies. Furthermore, the classical, SMAD-independent pathway of TGF-β receptors may engage in crosstalks with other signaling pathways, such as Wnt/β-catenin, Ras/RAF/MAPK, and PI3K/Akt/mTOR pathways, to play vital roles in carcinogenesis, and a proper understanding of the TGF- β signaling pathway in cancer progression would resolve controversies related to the signaling pathways [73,74]. 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 [75,76].

The Hippo Signaling Pathway: Hippo Pathway is an evolutionarily conserved major signaling pathway originally identified in fruit flies (Drosophila melanogaster) and controls contact inhibition and organ size development. It is a serine/threonine kinase signaling cascade and its dysregulation 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 malignant growth. The canonical Hippo pathway comprises 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 translocates 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 [77]. 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 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 [78.79].

Wnt/β-catenin Signaling Pathway: This signaling pathway 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-protein binding to the extracellular domain of a Frizzled (Fz) family receptor, a distinct family of GPCRs that generally do not involve activation of G proteins, to relay signals through the cell via different paths to influence a variety of cellular mechanisms critical to cancer development. The Wnt pathway has been formally divided into theβ-catenin dependent canonical pathway and the β-catenin independent, non-canonical Planar cellpolarity (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 activationof β- catenin preventing excessive cell growth and tumor formation. The APC/β-catenin pathwayis 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, indicating an overlap with several tumor-promoting pathways. Mutations that prevent the degradation of β-catenin, including certain mutations in β-catenin or the APC component of the β-catenin destruction complex and others distort the regenerative pathway to contribute to cancer progression and metastasis [80]. Deregulation of the signaling pathway results in alterations in cell growth and survival, maintenance of cancer stem cells, metastasis, and immunecontrol which have been linked to both solid and hematological tumors. The activation of the non-canonical pathway generally involves the recruitment of Rho family small GTPase that leadsto enzymatic rearrangements of the cytoskeleton and/or certain transcriptional activation of effector proteins. Both of these pathways essentially require the binding of Wnt proteins to the Frizzled receptors for the execution of the function.

The Wnt/Ca2+ signaling is followed by G-protein-activated phospholipase C activity leading to intracellular 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. Mutations of the APC gene are observed in about 80% of colon cancers where cancer stem cells (CSCs) are thought to play a critical role in metastasis and relapse, indicating the role of this signaling in maintaining CSC. The role of Wnt signaling in cancer immune evasion and drug resistance is well recognized, and identifying tumor-specific signaling intermediates as targets for drug action can be crucial to effective cancer therapy. Many different agents effectively targeting molecules of this signaling pathway are being explored for the efficacious treatment of different cancer types [81,82].

Hedgehog (Hh) Signaling Pathway: Hh is an evolutionarily conserved signaling pathway and one of a few signaling pathways frequently involved in intercellular communication. It is a key regulator of embryonic development that controls cell patterning, proliferation, and differentiation for organs developments in mammals as well as in the regeneration and maintenance of tissue homeostasis This pathway has frequently been associated with birth defects, stem cell renewal, and cancer. Hh signaling depends on three transmembrane receptor

proteins. Namely Patched, iHog, and Smoothened. Hh proteins are coded by at least three genes in vertebrates that include Sonic, Desert, and Indian hedgehog. 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. There are three different forms of the transcription factor, Gli1. Gli2 and Gli3 are present in vertebrates which may undergo proteasomal processing similar to that of the Wnt pathway to exert their effects in response to appropriate signals. The activated form of Gli moves to the nucleus to bind to their promoters leading to the transcription of the target genes. Mutational changes that lead to excessive activation of the Hh pathway have been implicated in different malignancies. Communication between Hh and major signaling pathways, such as Wnt, Notch, and TGF-β, play crucial roles in the pathophysiology of the disease. Several Hh signaling pathway inhibitors have been developed for a range of cancers, and a few agents are thought to be highly effective for patients with recurrent and advanced cancers [83].

Notch signaling pathways: It is a contact-dependent signaling pathway that has a major role in controlling cell fate decisions and regulating pattern formation during the renewal and development of most tissues and performs major tasks during the embryonic development of animals. Signaling is mediated through the Notch receptor protein, a single-pass transmembrane protein that undergoes successive proteolytic cleavage steps upon activation to perform its action. Notch is activated in a contact-dependent manner by the specific signal protein called Delta, present on the neighboring cell that leads to the cleavage and release of its cytoplasmic tail, notch intracellular domain (NCID) which translocates to the nucleus where it regulates expression of the target genes [84]. Notch signaling is associated with the regulation of many cellular processes like cell proliferation, survival, differentiation, and apoptosis through cell-to-cell communication crucial to the development of many tissues. The signaling pathway is a key regulator of self-renewal and differentiation of many cell types and is known to be an important regulator of Hematopoiesis. Notch acts as a context-dependent binary cell-fate-determining pathway and its hyperactivation has been implicated in the oncogenic stimulation of many solid and hematological cancers.

The Hh and Notch signaling pathways are the active regulators of communication between cells and are actively involved in EMT regulation that is critical to organ development, regeneration, stem cell maintenance, and tissue homeostasis. The self-renewal potential of cancer stem cells (CSCs) has been attributed to these signaling pathways crucial to maintaining CSCs in the tumor mass that causes disease progression, recurrence, and chemoresistance. Importantly, the Hippo pathway has been found to repress Wnt signaling stimulation which could induce cancer stems cell activities. In addition to that, 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 [85]. 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 presents the option to identify the signaling intermediates with confirmed hyperactivities as potential targets in anti-CSC drug discovery for effective cancer treatment. Selective targeting of these pathways along with other proliferative pathways such as the PI3K/Akt or RAS/RAF/MAPK pathways could prove to be an effective strategy for combination therapy of cancer [86, 87].

The NF-κB signaling pathway: This pathway 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 [88]. Constitutively activated NF-κB signaling may lead to inflammation-related disorders, and its role in pathological inflammation and cancer development is well recognized now [89]. 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 [90]. 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 [91,92]. 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 [93,94].

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 [95,96]. 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 [95]. cGAS–STING signaling may also induce autophagy and additionally communicate via p53, MAPK p38, and STAT3 signaling in a context-dependent manner [9]. 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 [97].

Rho/ ROCK signaling pathway: The components of the Rho/ Rho-kinase (ROCK) signaling pathway are established as the potential regulators of the cell's actin cytoskeleton and dynamics.

ROCKs (ROCK1 and ROCK2) belong to the AGC (PKA/ PKG/PKC) family of serine-threonine specific protein kinases which is a downstream effector of the small guanosine triphosphatase (GTPases), RhoA, B, and C, and actively participates in a variety of cellular activities controlled by the actin cytoskeleton including cell polarity, cell contraction, cell cycle progression, proliferation, motility, and invasion. Aberrant Rho/ROCK signaling has been convincingly implicated in several cancer types owing to its ability to enhance tumor growth, cell migration, metastasis, and extracellular matrix remodeling [98]. Molecular inhibitors are being developed to target ROCK1, ROCK2, or both, with high clinical value for the treatment of advanced solid cancers. Moreover, the different activities of ROCK in the immune system make it a potential target in cancer immunotherapy, so ROCK is thought to be of great value in cancer therapeutics. A deeper understanding of this pathway may add new dimensions to future precision cancer therapy [99]

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

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 [100]. 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 [101]. It forms the basis of precision medicine in general and is at the core of the development of precision oncology. The breakthroughs in high-throughput technologies in recent years have led to the rapid accumulation of large-scale omics cancer data and brought an evolving concept of “big data” in cancer the analysis of which requires huge computational resources with the potential to bring new insights into critical problems. The combination of big data, bioinformatics, and artificial intelligence is thought to lead to notable advances in translational research in cancer [102,103].

Artificial intelligence: Artificial intelligence (AI) encompasses multiple technologies with the common aim of computationally simulating human intelligence to solve complex problems. It is based on the principle that human intelligence can be defined in a way that a machine can easily mimic and execute tasks from the simpler to far more complex ones successfully [104]. Broadly referred to as computer programming enabled to perform specific tasks, the term may be applied to any machine that displays traits associated with human understanding, such as learning and problem-solving. In regular programming, data are processed with well-defined rules to bring solutions, whereas AI relies on the learning process to devise rules for the efficient processing of data to yield smart results. AI and related technologies have increasingly been prevalent in finance, security, and society, and are now being applied to healthcare as well [105]. It has been widely applied in precision medicine-based healthcare practices and is found to be greatly useful in medical oncology practice. 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 knowing 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 advances in NGS have 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, integrating multi-omics-related studies with artificial intelligence is the need of the hour and is likely to serve the purpose well with time. 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 for anticipated results. Thus, the advances in AI 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 are mostlikely to help many more problems in this direction to be resolved swiftly. In this way, AI is thought to be the future of precision oncology towards the prevention, detection, risk assessment,and treatment of cancer [106,107].

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 [108]. Therefore, the most common and purposeful application of traditional machine learning in healthcare seems to be in the area of precision medicine and is most suited for the data-driven identification of cancer states and designing treatment options that is crucial to precision oncology-based cancer treatment [109].

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, multi-omics-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 processing several pieces of information received from many different sources to translate into a particular reflex action. In DL, the same concept of a network of neurons is imitated on a machine learning platform to emulate human understanding to bring perfect solutions. The neurons are created artificially in a computer system and the data processing layers work together to create an artificial neural network where the working of an artificial neuron could be taken as like that of a neuron present in the brain. Thus, DL is designed to use a complex set of algorithms enabling it to process unstructured data such as documents, images, and text to find efficient results [110].

The effective development of drugs for the treatment of cancer is a major problem in cancer research and DL provides immense help to researchers in this regard. 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 the 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. Occupation-oriented pharmacology is the dominant paradigm of drug discovery for the treatment of cancer. It relies on the use of inhibitors that occupy the functional binding site of a protein and can disrupt protein interactions and their functions. 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 [111]. 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. 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 almost every known organism on the planet [112,113]. 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. A newly developed DL system called PocketMiner is an efficient tool for predicting the locations of bonding sites on proteins. Proteins exist in a state of dynamic equilibrium with their different conformational structures, including experimentally determined structures that may not have targetable pockets. PocketMiner uses graph neural networks to find hidden areas or pocket formation from a single protein and is thought to be 1,000 times faster than existing methods of finding binding sites on proteins. This technology has made researchers understand that around half of proteins that were earlier considered undruggable might have 'cryptic pockets' that could be targeted successfully by anticancer agents. The AI-based system finds multiple uses in cancer management like the prediction of treatment response, estimation of survival analysis, risk estimation, and treatment planning, and is becoming the central approach in precision oncology [114].

7. The Cancer Genome Atlas (TCGA) Program and Related Cancer Initiatives

The National Institutes of Health (NIH) has taken the lead role in cancer research and is the largest funder of cancer research in the world. The National Cancer Institute (NCI), the leading cancer research enterprise is part of NIH and is committed to exploiting basic cancer research into efficacious cancer therapies. In this regard, the Cancer Genome Atlas (TCGA) Program is the landmark cancer genomics program initiated by the NIH, and 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 is a joint effort by the NCI and the National Human Genome Research Institute (NHGRI), also a part of NIH, that began working in 2006 and has 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 [115,116]. Considering the genes and pathways affecting different cancer types and individual tumors vary considerably, a complete understanding of these alterations becomes essential to identify vulnerabilities and discover precise therapeutic solutions. A comprehensive analysis of tumors based on their genomic studies must reveal the alterations in signaling pathways indicating patterns of vulnerabilities and the means to identify prospective targets for the development of personalized treatments and new combination therapies. The TCGA ResearchNetwork has profiled and analyzed a large number of human tumors to discover molecular aberrations at the DNA, RNA, protein, and epigenetic levels and thereby provided reliable diagnostic and prognostic biomarkers for different cancer types since then.

As our understanding of biochemical signaling has grown and the range of possible

treatment options expands, it is essentially required to have biomarkers to accurately predict how patients will respond to specific treatment regimens, which is a vital need for precision oncology. Circulating DNA and extracellular vesicles are abundantly released by cancer cells that can be obtained by liquid biopsies and are excellent sources of a variety of molecular markers. Molecular profiling of these markers can be used to gain crucial information regarding cancer development including tumor heterogeneity. Genomic analysis of tumors has certainly become the mainstay in cancer care, and applying it to oncological practice needed a clinical support system that could swiftly predict the clinical implications associated with specific mutations. It led to the development of OncoKB, an expert-guided precision oncology knowledge base developed at Memorial Sloan Kettering Cancer Center (MSKCC), in New York which is among the first to have been recognized as the NCI-Designated Cancer Centers as part of the national cancer program of the federal govt. that started in 1971. OncoKB's curated list of cancer genes with detailed comments is available on its public web resource (http://oncokb.org, which has been incorporated into the cBioPortal for Cancer Genomics (https://www.cbioportal.org/) to provide visualization, analysis, and download of large-scale cancer genomics data sets allowing researchers to gain a thorough understanding of the genomic alterations involved in cancer development. The public cBioPortal site is hosted by the Center for Molecular Oncology at MSKCC and maintained by a multi-institutional team consisting of MSK and others. 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 precise techniques to fulfill the purpose involved with the big-data studies satisfactorily [117,118].

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 help gain insights into 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 [119,120]. It is based on the consideration that possible observable combinations of those mutations must converge to a few hallmark signaling pathways and associated networks responsible for cancer development. In this way, the proposed framework aims to analyze the available 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 progression and direct treatment planning accordingly. In this regard, 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 [121,122]. Analyzing over 11,000 tumors from the most prevalent forms of cancer, and focusing on how germline and somatic variants collaborate in cancer progression, the Pan-Cancer Atlas has so far provided a most comprehensive and in-depth understanding of how and why tumors arise in humans [123,124].

The synchronizing view of 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 also present novel biological and clinical insight for cancer stem cell-targeted therapies [125,126]. 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 receive precisely designed treatment for cancer. 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.

Besides that, the Cancer Cell Mapping Initiative (CCMI), originally founded in 2015 by researchers from the University of California, San Francisco, and the University of California, San Diego, has been dedicated to generating complete maps of major protein-based genetic interactions underlying cancer progression and attempts to develop computational methods using these maps to identify novel drug targets and patient groups with common outcomes. It 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 [127]. 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 [128]. Furthermore, the Broad Institute of MIT and Harvard's Cancer Dependency Map (DepMap)initiative, an academic-industrial partnership program formally announced in 2019, is devoting its research to accelerate precision cancer medicine by creating a comprehensive map of tumor vulnerabilities and identifying key biomarkers of cancer. DeepMap initiative is focused on screening thousands of cancer cell lines by the use of RNA interference (RNAi) and CRISPR- Cas9 loss-of-function gene-editing strategies to identify genes whose expression may have been found to be essential for cancer cell development. CRISPR-Cas9 gene editing is an efficient method for genome modification for nearly all cell types. CRISPR editing and screening have emerged as powerful tools for investigating almost all aspects of cellular behaviors and have greatly impacted our understanding of cancer biology and continue to contribute to new discoveries.

A related project called, Cancer Cell Line Encyclopedia (CCLE) project was initiated as a collaboration between the Broad Institute, and the Novartis Institutes for Biomedical Research in 2008 aimed at large-scale genetic characterization of thousands of cancer cell lines to link characteristic genetic alterations with distinct pharmacologic vulnerabilities, and to translate cell line integrative genomics into cancer patient stratification. By access to critical genomic data such as gene mutation, copy number variation, gene expression, and methylation profiles from the CCLE, scientists can now predict novel synthetic lethality and identify new molecular markers whose selective targeting can control cells that possess specific genetic mutations. In this way, the initiative has provided a rigorous foundation on which to study genetic variants, and candidate targets, design anticancer agents and identify new markers-driven cancer diagnoses and therapies [129]. By all such means, the field of cancer genomics can be seen as constantly evolving to help cancer-causing changes be identified to gain a better understanding of the molecular basis of cancer growth, metastasis, and drug resistance, and translate cancer

research into new cancer therapeutics.

8. Single-cell Technology to Unmask Tumor Heterogeneity

The tumor is an abnormal mass of tissue that appears due to unregulated growth and division ofcells which successfully avoid senescence. A tumor is benign till it is limited to its original position and becomes malignant or cancerous when capable of growing and spreading to other parts ofthe body. Tumor heterogeneity is a hallmark property of cancer development and broadly refersto the differences between tumors of the same type in different patients, the differences betweena primary and a secondary tumor, and the differences in genomic and phenotypic profiles displayed by cells within a single tumor. 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]. Tumor heterogeneity appears to be a critical phenomenon in the history of individual cancers, as its translational significance may reflect on tumor progression, disease recurrence, treatment response, and resistance [132]. Recent investigations on drug resistance and tumor heterogeneity have confirmed 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 advanced treatment strategies for cancer [133,134]. More precisely the cellular composition of a tumor is known, the underlying mechanism of disease progression is understood, and/or molecules and pathways involved in the process are identified, and more specific therapeutic strategies could be devised to get the desiredresult. It is the stated goal of precision oncology 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 mutational profile of the affected cells to better understand the molecular consequences of different variants presentin the tumor. 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 identifying somatic SVs, understanding genomic rearrangements and unmask tissue heterogeneity. Moreover, single-cell sequencing can also be combined with CRISPR knockout screening 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 to fully understand the underlying cellular events [137]. Combining the CRISPR-Cas system with single-cell techniques for studying gene functions with the concurrent use of single-cell resolution techniques, such as flow cytometry, microfluidics, manual cell picking, or micromanipulation, can be exploited in cancer research in many ways, including identifying novel drug targets, studying unknown mechanisms of action of drugs and designing treatment regimen [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 tumor suppressor genes. Abnormal epigenetic changes are usually influenced by aging, viruses, and dietary and environmental factors that frequently contribute to cancer development. 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 single-cell epigenome profiling holds great possibilities for deciphering the cellular states and characterizing tumor heterogeneity with an option for therapeutic interventions to pin specific mutations having profound effects on epigenetic pathways. 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.

Single-cell sequencing technologies have largely been successful in leading scientists to understand the cell types and features associated with the tumor yet, the spatial context of this development is essential to better understand how cells organize and communicate across the tissue to fully unlock the repertoire of tumor heterogeneity. It requires 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. This is an essential part of spatial biology and adds another dimension to single-cell analysis to unmask tumor heterogeneity [140,141]. Spatial biology simply tries 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 multi-omics technologies allowing researchers to measure all the gene activity in a tissue sample and assay the genetic information of single cells within their native tissue environment [142,143]. The growing ability to demonstrate the role and function of distinct cell types present in the tissue has paved the way for a new understanding of the tissue-specific cellular pathways and interactions that lead to cancer manifestation.

Thus, molecular analysis of cancer cells based on single-cell technologies aims to present an accurate picture of the most recent developments regarding changes in genes and proteins responsible for alterations in cellular processes, enabling a better understanding of prognosis and pathways of development of cancer. New advances in multi-omics techniques powered by AI h now enable researchers to integrate genomic, transcriptomic, epigenomic, and other related data to gain the most accurate information on the activity state of individual genes and proteins to reveal the 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 likely to streamline future research directions.

9. Precision Oncology and Targeted Drug Therapy of Cancer

Targeted drug therapy is the form of cancer therapeutics that targets specific genes and proteins of cancer cell reprogramming, the signaling molecules, and others in the tumor microenvironment that contribute to cancer development. This contrast with the single-target approach employed in chemotherapy to primarily target and kill actively dividing cancer cells with serious side effects and so the emergence of targeted drug therapy can be seen as a natural outcome of decades of studies on molecular reprogramming of affected cells in different cancers. Some noticeable breakthroughs have come in certain cancers as a renewed understanding of the signaling pathways underlying cancer development has led to the development of specific targeted drugs that have really revolutionized the treatment of cancer. This form of cancer therapy can be thoroughly optimized by means of precision oncology that enables taking advantage of genomic profiling of patient samples for insights into the mutational changes underlying pathway alterations responsible for cancer initiation and progression [146]. Precision oncology-based treatment strategies pledge to diagnose and prognosis the disease using specific molecular-level information about a patient's tumor to treat the ill with desired results. Inthis way, it qualifies to be a theranostic approach to cancer treatment satisfactorily. The term, theranostics literally means a combination of diagnosis and therapeutics and refers to the pairing of diagnostic methods such as the proteogenomics approach to biomarker discovery, with appropriate therapeutic interventions for effective management of the disease. Theranostics focuses on patient-centered care and thus provides a transition from conventional to personalized medicine for targeted, efficient and safe pharmacotherapy relevantly applicable in precision oncology [147,148].

The anticancer drugs employed in targeted therapy are mainly 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 [149]. They are broadly classified as monoclonal antibodies (mAbs) and small-molecule drugs. The small molecule drugs are designed to directly approach the cell membrane and interact with targets inside the cell and usually inhibit the enzymatic activity of target proteins such as the proteasome complex, cyclin-dependent kinases and a variety of signaling proteins. Kinase family proteins such as tyrosine kinases, Rho kinase, Bruton tyrosine kinase, ABL kinases, NAK kinases, etc. play an essential role in modulating signaling pathways associated with cancer progression and therefore constitute a valuable source of biological targets against cancers (Table 1). A type of targeted therapy, called tumor-agnostic therapy uses drugs and other substances to target cancer-specific genetic changes or markers to treat the problem without requiring focusing on the cancer type or where the disease may have started in the body.

Table 1. List of Protein Kinase Inhibitors approved by FDA.
(NRY, non-receptor protein-tyrosine kinase; RTK, receptor protein-tyrosine kinase; S/T, protein-serine/threonine kinase; T/Y, dual-specificity protein kinase)

Protein kinase inhibitor	Approval year	Primary targets	Target kinase family	Indications
Abemaciclib	2017	CDK4/6	S/T	Breast cancer
Acalabrutinib	2017	BTK	NRY	Lymphoma

Afatinib	2013	ErbB1/2/4	RTK	Lung cancer
Alectinib	2015	ALK, RET	RTK	Lung cancer
Avapritinib	2020	PDGFR	RTK	Gastrointestinal Cancer
Axitinib	2012	VEGFR1/2/3	RTK	Kidney cancer
Binimetinib	2018	MEK1/2	T/Y	Melanoma
Bosutinib	2012	BCR-Abl	NRY	Leukemia
Brigatinib	2017	ALK	RTK	Lung cancer
Cabozantinib	2012	RET, VEGFR2	RTK	Thyroid. kidney, hepatocellular cancer
Capmatinib hydrochloride	2020	c-MET	RTK	Lung cancer
Ceritinib	2014	ALK	RTK	Lung cancer
Cobimetinib	2015	MEK1/2	T/Y	Melanoma
Crizotinib	2011	ALK, ROS1	RTK	Lung cancer
Dabrafenib	2013	B-Raf	S/T	Melanoma; lung, thyroid Cancer
Dacomitinib	2018	EGFR	RTK	Lung cancer
Dasatinib	2006	BCR-Abl	NRY	Leukemia
Encorafenib	2018	B-Raf	S/T	Melanoma, colorectal cancer
Entrectinib	2019	TRKA/B/C, ROS1	RTK	Lung cancer; solidTumors
Erdafitinib	2019	FGFR1/2/3/4	RTK	Urothelial carcinoma
Erlotinib hydrochloride	2004	EGFR	RTK	Lung, Pancreatic cancer
Everolimus	2009	FKBP12/mTOR	S/T	Breast, kidney cancer, Neuroendocrine tumors
Fedratinib	2019	JAK2	NRY	Myelofibrosis
Futibatinib	2022	FGFR2	RTK	Cholangiocarcinomas
Gefitinib	2003	EGFR	RTK	Lung cancer
Gilteritinib	2018	Flt3	RTK	Leukemia
Ibrutinib	2013	BTK	NRY	Lymphoma

Imatinib mesylate	2001	BCR-Abl	NRY	Leukemia; Gastrointestinal
Infigratinib	2021	FGFRs	RTK	Cholangiocarcinoma
Lapatinib ditosylate	2007	ErbB1/2/HER2	RTK	Breast cancer
Larotrectinib	2018	TRKA/B/C	RTK	Solid tumors
Lenvatinib	2015	VEGFR, RET	RTK	Hepatocellular, endometrial, Thyroid, Kidney cancer
Lorlatinib	2018	ALK	RTK	Lung cancer
Midostaurin	2017	Flt3	RTK	Leukemia
Mobocertinib	2021	EGFR with exon 20 insertions	RTK	Lung cancer
Neratinib	2017	ErbB2/HER2	RTK	Breast cancer
Nilotinib	2007	BCR-Abl	NRY	Leukemia
Osimertinib	2015	EGFR T790M	RTK	Lung cancer
Pacritinib	2022	JAK2	RTK	Myelofibrosis
Palbociclib	2015	CDK4/6	S/T	Breast cancer
Pazopanib hydrochloride	2009	VEGFR1/2/3	RTK	Kidney cancer; soft tissue sarcoma
Pemigatinib	2020	FGFR2	RTK	Cholangiocarcinoma
Pexidartinib	2019	CSF1R	RTK	Tenosynovial giant cell tumor
Pirtobrutinib	2023	BTK	NRY	Lymphoma
Ponatinib hydrochloride	2012	BCR-Abl	NRY	Leukemia
Pralsetinib	2020	RET	RTK	Lung cancer
Quizartinib	2023	FLT3/STK1	RTK	Leukemia
Regorafenib	2012	VEGFR1/2/3	RTK	Gastrointestinal, Colorectal, Hepatocellular cancer
Ribociclib	2017	CDK4/6	S/T	Breast cancer
Ripretinib	2020	KIT/PDGFR	RTK	Gastrointestinal cancer
Ruxolitinib phosphate	2011	JAK1/2/3, Tyk	NRY	Myelofibrosis

Selpercatinib	2020	RET	RTK	Lung, thyroid cancer
Selumetinib	2020	MEK1/2	T/Y	Neurofibroma
Sorafenib tosylate	2005	VEGFR1/2/3	RTK	Thyroid, Kidney, Hepatocellular cancer
Sunitinib malate	2006	VEGFR2	RTK	Gastrointestinal, kidney, pancreatic cancer
Temsirolimus	2007	FKBP12/mTOR	S/T	kidney cancer
Tepotinib	2021	Met	RTK	Lung cancer
Tivozanib	2021	VEGFR2	RTK	kidney cancer
Trametinib	2013	MEK1/2	T/Y	Melanoma
Trilaciclib	2021	CDK4/6	S/T	Lung cancer
Tucatinib	2020	ErbB2/HER2	RTK	Breast cancer
Vandetanib	2011	VEGFR2	RTK	Thyroid cancer
Vemurafenib	2011	B-Raf	S/T	Melanoma; histiocytic sarcoma
Zanubrutinib	2019	BTK	NRY	Lymphoma

Therapeutic targeting of DNA damage response (DDR) signaling is another emerging field of targeted cancer therapy that exploits the options of targeting cancer cells with exceeding deficiencies in homologous recombination (HR) signaling which includes 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. These enzymes are essentially involved in the process of single-strand break (SSB) repair whose failure leads to the conversion of SSB into double-strand breaks (DSB) requiring repair by HR to prevent cell death. Such lethal genetic interactions, known as synthetic lethality, can be exploited to develop anticancer therapeutics and the enzymes of DDR signaling fit the needs satisfactorily. Overexpression of these proteins has been witnessed in different cancer types such as pancreatic, prostate, breast, ovarian, and oral cancers, providing scope 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 safely. [150,151].

The therapeutic mAbs are modified monoclonal antibodies that target antigens found on the cancer cells or cytotoxic T-lymphocytes in targeted cancer therapy. mAbs are important in cancer treatment as they may be exploited for potentiating the natural immune system by

successfully mutualizing changes in immunogenicity of the affected cells during oncogenesis. The mAbs may be designed to coat the cancer cells to be opsonized and destroyed by the immune cell, block the activity of different cancer-specific antigens called neoantigens, generated by cancer cells, or inhibit the activities of immune checkpoint proteins that promote immune evasion in cancer development [152,153]. Several immune checkpoint proteins are expressed by immune cells, such as T cells, and cancer cells capable of binding with other partner proteins to help cancer cells escape immune responses. Their activation limits vital immune cell activities like T-cell infiltration and other effector cell functions resulting in tumor formation. CTLA-4 is a checkpoint protein present on the T-cell surface that binds to another protein called B7, preventing T cells from killing other target cells, including cancer cells. Certain mAbs, also called anti-CTLA4 monoclonal antibodies, are used to block CTLA-4 and are widely used as immune checkpoint inhibitors in a variety of human cancers. Different forms of monoclonal antibody-based therapy have proven to be efficacious in cancer treatment and are becoming increasingly important tools in targeted cancer therapy [154,155]. Importantly, cancer cells express a number of protein antigens that can be recognized by cytotoxic T lymphocyte (CTL) T cells, thus providing means for CTL-mediated cancer therapy. Targeting transformed cells by CTL may be crucial to the prevention of both hematological and solid tumors and its roles are being explored in cancer immunotherapy. T-cell transfer therapy, also called adoptive immunotherapy or immune cell therapy is a new form of cancer treatment designed to exploit enhanced anti-tumor immune response of the tumor antigen-specific CTL found in the tumors, and has been tried against neoantigen-possessing cells effectively in recent times. Two types of T-cell transfer therapy, tumor-infiltrating lymphocytes or TIL therapy and CAR T-cell therapy are in use, and both involve harvesting autologous T cells infiltrated into the tumor, growing largenumbers of these cells in vitro, and administering to the patient for desired results. CAR T-cell therapy is similar to TIL therapy except that the T cells are designed to express a type of protein known as CAR (CAR for chimeric antigen receptor) to target specific antigens expressed in cancer cells in the body. Although CAR T cells have significantly improved the landscape for hematological malignancies, it has shown limited results in solid tumors as the solid tumors present certain obvious barriers to adoptive T-cell transfer and localization, but a variety of approaches are being deliberated to overcome these barriers to increase its specificity, efficacy, and safety in the treatment of different malignancies. The development of CAR T cell therapy forsolid tumors has been impaired also because most target antigens are common with normal cells.Research is being directed to develop a ‘toolbox’ of novel chimeric antigen receptors (CARs) that could be programmed to use logic to discriminate between normal and cancerous cells to prevent toxicity. This development could help to overcome some of the barriers to the application of CAR-T cells against solid tumors.

Furthermore, therapeutic cancer vaccines, such as the dendritic cell (DC) vaccine, peptide vaccine, and RNA-based neoantigen vaccines have been developed for inducing CTLs against the antigens in cancer patients and have shown encouraging results. These vaccines can be designed to induce the production of biomolecules capable of targeting the shared antigens expressed by cancer cells through appropriate immune response and, are being investigated for their efficacy as neoantigen-targeted individualized cancer vaccines. Dendritic cells (DCs) are specialized Antigen-presenting cells (APCs) known for their ability to present antigens to T cells, and this property of DCs has been exploited for their application in therapeutic cancer vaccines which have been shown to induce protective anti-tumor activities. [156,157]. Besides that, the transposable elements (REs) usually present in the tumor microenvironment are of potential therapeutic importance to create a pan-cancer vaccine that can aid in the prevention of a range of

cancers. There is an enumerable number of regions with TEs involved with the expression of proteins in the cancer cell. Many of these are shared across tumors of the same type and could provide means for destruction by the immune system. 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 results. Thus, immunotherapy remains the frontline area of cancer research, and precision oncology will be focused on immunotherapy accordingly.

As discussed earlier, a major concern in cancer therapeutics is the proper drug delivery to the affected cells and tissue for the desired 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 (NP)-based systems can be programmed to recognize cancerous cells for selective and accurate drug delivery with increased drug localization, cellular uptake, and bioavailability, avoiding encounters with healthy cells. The newly developed quantum dots (QDs) are the class of heterogeneous fluorescent nanoparticle, nanoscale materials with sizes ranging from 1 to 10 nm, with unique optical properties and optimal surface chemical properties to link with targets such as antibodies, peptides, and other small molecule drugs. Named so as the photoluminescent nanostructures can have fully quantized energy states with superior fluorescence characteristics, they are thought to be more specific and effective methods with wide applications in the diagnostics and molecular targeting of the transformed cells. The NP-based drug delivery system, in general, displays better pharmacokinetic and pharmacodynamic profiles including efficient targeting of cancer cells and reduction in side effects, they are sure to serve the needs of precision oncology-based therapy satisfactorily [158,159]. Further, antibody-drug conjugates (ADC) are a fast-expanding therapeutic strategy designed to selectively deliver drugs to cancer cells. ADCs are monoclonal antibodies linked with small molecule cytotoxic drugs through a chemical linker capable of approaching the cancer cells and attaching 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 featuresof antigen-antibody specificity for efficient drug delivery and are considered to be the magic bullets in targeted cancer therapy [10, 161]. In this way, precision oncology seems to be the best fit for strategizing effective means of targeted drug therapy by exploiting the genomic peculiarities of individuals or a cohort of patients for effective personalized cancer treatment (Fig. 2). Itwill remain dedicated to studying the genetic profile of cancer cells to gain a thorough understanding of the alterations in key signaling pathways and related molecular events during cancer progression, therapy resistance, and recurrence to help improve targeted cancer therapy (Suppl. 1 & 2).

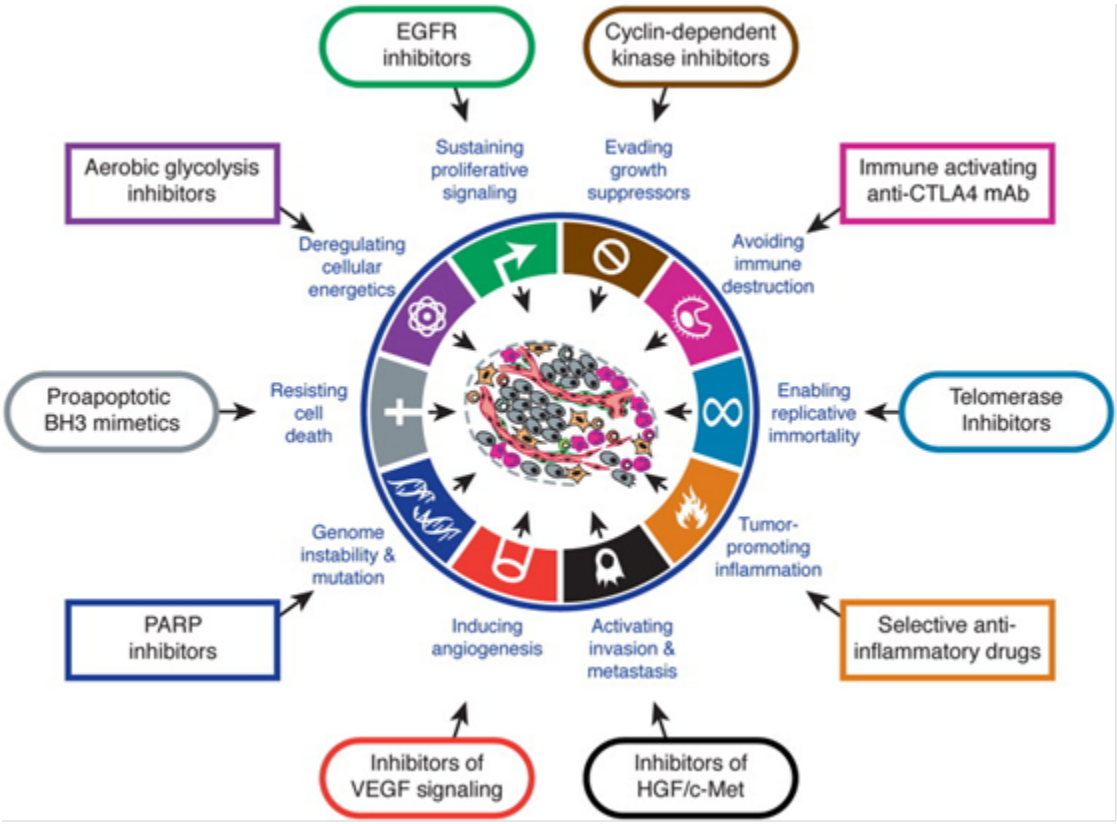

Figure 2. Therapeutic Targeting of the Hallmarks of Cancer
Therapeutic agents that can mitigate the acquired capabilities necessary for tumor growth and cancer progression are being developed for clinical use in treating different cancer types. These drugs are being developed in clinical trials to target each of the emerging neoplastic characteristics and the enabling hallmarks capabilities towards 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]. With permission from Elsevier)

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 willbe needed for future research, drug discovery, and diagnostics to fully unlock its potential and for their application in the management of cancer. Let us not forget that the socioeconomic burden of cancer remains high as the treatment options for most common cancers have been limited so far and is an indication for a renewed approach to expedite 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 extentby 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 [162,163]. Moreover, the move from tissue-based cancer-specific treatments to genome-based targeted treatments entails the reuse of anticancer drugs prescribed for one type of cancer to treat other cancer types as well.It is envisaged that, with the ever-greater understanding of cell signaling mechanisms and geneticalterations in carcinogenesis, considerable progress in cancer treatment will be realized in the near future. Considering that academia, industries, and civil society will be working in

tandem tocater to the contemporary 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 system as a whole [164,165].

10. 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 not very effective in the end. Further, 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. Besides that, 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. Importantly, drug resistance has traditionally been a serious problem in cancer treatment, but the emergence of targeted drug therapy based on precision oncology can greatly improve outcomes. The evolution of gene detection methods, liquid biopsy, and single-cell sequencing technology could facilitate deciphering the molecular mechanism of tumor drug resistance to help develop updated and effective anticancer agents in response to drug resistance. Thus, precision oncology, which relies on the genomic specificity of individuals for successful targeting of the most specific pathways involved in disease progression, is best suited to ensure precise treatment of the disease. This is in fact a natural outcome of cancer genome research, the level of support from multi-omics platforms is most encouraging and it is poised to satisfactorily achieve the intended goal of the cancer initiatives. The growing success of this form of treatment is sure to further strengthen our belief in the possibility of an effective treatment for cancer and it must be made available to an increasing number of people with cancer in order to achieve the goals over time.

Declarations:

Acknowledgements: I acknowledge the consistent departmental support received from the School of Bio Sciences & Technology, Vellore Institute of Technology, Vellore, Tamil Nadu, India, leading to the completion of this work with time.

Authors' contributions: Not applicable

Competing interests: Not applicable

Informed Consent Statement: Not applicable.

Funding: Not applicable

Data Availability Statement: No new data was created, the data analyzed in this study is present in the text and as supplementary materials.

References:

1. Ma X, Yu H. Global burden of cancer. Yale J Biol Med. 2006 Dec;79(3-4):85-94. PMID: 17940618; PMCID: PMC1994799.

2. Clegg LX, Reichman ME, Miller BA, Hankey BF, Singh GK, Lin YD, Goodman MT, Lynch CF, Schwartz SM, Chen VW, Bernstein L, Gomez SL, Graff JJ, Lin CC, Johnson NJ, Edwards BK. Impact of socioeconomic status on cancer incidence and stage at diagnosis: selected findings from the surveillance, epidemiology, and end results: National Longitudinal Mortality Study. Cancer Causes Control. 2009 May;20(4):417-35. doi: 10.1007/s10552-008-9256-0. Epub 2008 Nov 12. PMID: 19002764; PMCID: PMC2711979.

3. Sung, H, Ferlay, J, Siegel, RL, Laversanne, M, Soerjomataram, I, Jemal, A, Bray, F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021: 71: 209- 249. https://doi.org/10.3322/caac.21660

4. Siegel, RL, Miller, KD, Fuchs, HE, Jemal, A. Cancer statistics, 2022. CA Cancer J Clin. 2022. https://doi.org/10.3322/caac.21708

5. Kaluzny AD, O'Brien DM. How vision and leadership shaped the U.S. National Cancer Institute's 50-year journey to advance the evidence base of cancer control and cancer care delivery research. Health Policy Open. 2020 Dec;1:100015. doi: 10.1016/j.hpopen.2020.100015. Epub 2020 Oct 13. PMID: 33073235; PMCID: PMC7550860.

6. Haier, J.; Schaefers, J. Economic Perspective of Cancer Care and Its Consequences for Vulnerable Groups. Cancers 2022, 14, 3158. https://doi.org/10.3390/ cancers14133158

7. Rajpal S, Kumar A, Joe W. Economic burden of cancer in India: Evidence from cross-sectional nationally representative household survey, 2014. PLoS One. 2018 Feb 26;13(2):e0193320. doi: 10.1371/journal.pone.0193320. PMID: 29481563; PMCID: PMC5826535.

8. Cuomo RE, Mackey TK. Policy and governance solutions for ensuring equitable access to cancer medicines in low- and middle-income countries. Ann Transl Med. 2018 Jun;6(11):224. doi: 10.21037/atm.2018.04.26. PMID: 30023387; PMCID: PMC6035971.

9. Cho H, Mariotto AB, Schwartz LM, Luo J, Woloshin S. When do changes in cancer

survival mean progress? The insight from population incidence and mortality. J Natl Cancer Inst Monogr. 2014 Nov;2014(49):187-97. doi: 10.1093/jncimonographs/lgu014. PMID: 25417232; PMCID:PMC4841163.

10. Pilleron, S, Soto-Perez-de-Celis, E, Vignat, J, et al. Estimated global cancer incidence in the oldest adults in 2018 and projections to 2050. Int. J. Cancer. 2021; 148: 601– 608. https://doi.org/10.1002/ijc.33232

11. Rahib L, Wehner MR, Matrisian LM, Nead KT. Estimated Projection of US Cancer Incidence and Death to 2040. JAMA Netw Open. 2021 Apr 1;4(4):e214708. doi: 10.1001/jamanetworkopen.2021.4708. PMID: 33825840; PMCID: PMC8027914.

12. Bayat Mokhtari R, Homayouni TS, Baluch N, Morgatskaya E, Kumar S, Das B, Yeger H. Combination therapy in combating cancer. Oncotarget. 2017 Jun 6;8(23):38022-38043. doi: 10.18632/oncotarget.16723. PMID: 28410237; PMCID: PMC5514969.

13. Kumari S, Sharma S, Advani D, Khosla A, Kumar P, Ambasta RK. Unboxing the molecular modalities of mutagens in cancer. Environ Sci Pollut Res Int. 2022 Sep;29(41):62111-62159. doi: 10.1007/s11356-021-16726-w. Epub 2021 Oct 5. PMID: 34611806; PMCID: PMC8492102.

14. Basu AK. DNA Damage, Mutagenesis and Cancer. Int J Mol Sci. 2018 Mar 23;19(4):970. doi: 10.3390/ijms19040970. PMID: 29570697; PMCID: PMC5979367.

15. Yates, L., Campbell, P. Evolution of the cancer genome. Nat Rev Genet 13, 795–806 (2012). https://doi.org/10.1038/nrg3317

16. Sharma S, Kelly TK, Jones PA. Epigenetics in cancer. Carcinogenesis. 2010 Jan;31(1):27-36. doi: 10.1093/carcin/bgp220. Epub 2009 Sep 13. PMID: 19752007; PMCID: PMC2802667.

17. You JS, Jones PA. Cancer genetics and epigenetics: two sides of the same coin? Cancer Cell. 2012 Jul 10;22(1):9-20. doi: 10.1016/j.ccr.2012.06.008. PMID: 22789535; PMCID: PMC3396881.

18. Geeleher P, Huang RS. Exploring the Link between the Germline and Somatic Genome in Cancer. Cancer Discov. 2017 Apr;7(4):354-355. doi: 10.1158/2159-8290.CD-17-0192. PMID: 28373166; PMCID: PMC5404740.

19. Chang HY. Personal regulome navigation of cancer. Nat Rev Cancer. 2021 Oct;21(10):609-610. doi: 10.1038/s41568-021-00381-x. PMID: 34172966; PMCID: PMC9169632.

20. Zhang X, Meyerson M. Illuminating the noncoding genome in cancer. Nat Cancer. 2020 Sep;1(9):864-872. doi: 10.1038/s43018-020-00114-3. Epub 2020 Sep 14. PMID: 35121955.

21. Doroshow DB, Doroshow JH. Genomics and the History of Precision Oncology. Surg Oncol Clin N Am. 2020 Jan;29(1):35-49. doi: 10.1016/j.soc.2019.08.003. Epub 2019 Oct 29. PMID: 31757312; PMCID: PMC6878897.

22. Senft D, Leiserson MDM, Ruppin E, Ronai ZA. Precision Oncology: The Road Ahead. Trends Mol Med. 2017 Oct;23(10):874-898. doi: 10.1016/j.molmed.2017.08.003. Epub 2017 Sep 5. PMID: 28887051; PMCID: PMC5718207.

23. Pfohl U, Pflaume A, Regenbrecht M, Finkler S, Graf Adelmann Q, Reinhard C, Regenbrecht CRA, Wedeken L. Precision Oncology Beyond Genomics: The Future Is Here—It Is Just Not Evenly Distributed. Cells. 2021; 10(4):928. https://doi.org/10.3390/cells10040928

24. Song, I.-W.; Vo, H.H.; Chen, Y.-S.; Baysal, M.A.; Kahle, M.; Johnson, A.; Tsimberidou, A.M. Precision Oncology: Evolving Clinical Trials across Tumor Types. Cancers 2023, 15, 1967. https://doi.org/10.3390/cancers15071967

25. Advani D, Sharma S, Kumari S, Ambasta RK, Kumar P. Precision Oncology, Signaling, and Anticancer Agents in Cancer Therapeutics. Anticancer Agents Med Chem. 2022;22(3):433-468. doi: 10.2174/1871520621666210308101029. PMID: 33687887.

26. van Dijk EL, Auger H, Jaszczyszyn Y, Thermes C. Ten years of next-generation sequencing technology. Trends Genet. 2014 Sep;30(9):418-26. doi: 10.1016/j.tig.2014.07.001. Epub 2014 Aug 6. PMID: 25108476.

27. Diacofotaki, Anna, Axelle Loriot, and Charles De Smet. 2022. "Identification of Tissue-Specific Gene Clusters Induced by DNA Demethylation in Lung Adenocarcinoma: More Than Germline Genes" Cancers 14, no. 4: 1007. https://doi.org/10.3390/cancers14041007

28. Jafri, M.A., Ansari, S.A., Alqahtani, M.H. et al. Roles of telomeres and telomerase in cancer,

and advances in telomerase-targeted therapies. Genome Med 8, 69 (2016). https://doi.org/10.1186/s13073-016-0324-x

29. Bielski, C.M., Taylor, B.S. Homing in on genomic instability as a therapeutic target in cancer. Nat Commun 12, 3663 (2021). https://doi.org/10.1038/s41467-021-23965-5

30. Anwar, S.L.; Wulaningsih, W.; Lehmann, U. Transposable Elements in Human Cancer: Causes and Consequences of Deregulation. Int. J. Mol. Sci. 2017, 18, 974. https://doi.org/10.3390/ijms18050974

31. Fox EJ, Prindle MJ, Loeb LA. Do mutator mutations fuel tumorigenesis? Cancer Metastasis Rev. 2013 Dec;32(3-4):353-61. doi: 10.1007/s10555-013-9426-8. PMID: 23592419; PMCID: PMC3987827.

32. Saito, S.; Ku, C.-C.; Wuputra, K.; Pan, J.-B.; Lin, C.-S.; Lin, Y.-C.; Wu, D.-C.; Yokoyama, K.K. Biomarkers of Cancer Stem Cells for Experimental Research and Clinical Application. J.Pers. Med. 2022, 12, 715. https://doi.org/10.3390/jpm12050715

33. Tan, B., Park, C., Ailles, L. et al. The cancer stem cell hypothesis: a work in progress. Lab Invest 86, 1203–1207 (2006). https://doi.org/10.1038/labinvest.3700488

34. Gupta, P.K.; Saraff, M.; Gahtori, R.; Negi, N.; Tripathi, S.K.; Kumar, J.; Kumar, S.; Aldhayan, S.H.; Dhanasekaran, S.; Abomughaid, M.M.; Dua, K.; Gundamaraju, R.; Ojha, S.; Ruokolainen, J.; Jha, N.K.; Kesari, K.K. Phytomedicines Targeting Cancer Stem Cells: Therapeutic Opportunities and Prospects for Pharmaceutical Development. Pharmaceuticals 2021, 14, 676. https://doi.org/10.3390/ph14070676

35. Walcher L, Kistenmacher AK, Suo H, Kitte R, Dluczek S, Strauß A, Blaudszun AR, Yevsa T, Fricke S, Kossatz-Boehlert U. Cancer Stem Cells-Origins and Biomarkers: Perspectives for Targeted Personalized Therapies. Front Immunol. 2020 Aug 7;11:1280. doi: 10.3389/fimmu.2020.01280. PMID: 32849491; PMCID: PMC7426526.

36. Reya, T., Morrison, S., Clarke, M. et al. Stem cells, cancer, and cancer stem cells. Nature 414, 105–111 (2001). https://doi.org/10.1038/35102167

37. Kesh K, Gupta VK, Durden B, Garrido V, Mateo-Victoriano B, Lavania SP, Banerjee S. Therapy Resistance, Cancer Stem Cells and ECM in Cancer: The Matrix Reloaded. Cancers (Basel). 2020 Oct 21;12(10):3067. doi: 10.3390/cancers12103067. PMID: 33096662; PMCID:

PMC7589733.
38. Kulsum S, Raju N, Raghavan N, Ramanjanappa RDR, Sharma A, Mehta A, Kuriakose MA,Suresh A. Cancer stem cells and fibroblast niche cross talk in an in-vitro oral dysplasia model. Mol Carcinog. 2019 May;58(5):820-831. doi: 10.1002/mc.22974. Epub 2019 Jan 31. PMID: 30644602.

39. Dunn GP, Old LJ, Schreiber RD. The immunobiology of cancer immunosurveillance and immunoediting. Immunity. 2004 Aug;21(2):137-48. doi: 10.1016/j.immuni.2004.07.017. PMID: 15308095.

40. Clara JA, Monge C, Yang Y, Takebe N. Targeting signalling pathways and the immune microenvironment of cancer stem cells - a clinical update. Nat Rev Clin Oncol. 2020 Apr;17(4):204-232. doi: 10.1038/s41571-019-0293-2. Epub 2019 Dec 2. PMID: 31792354.

41. Wheeler DA, Wang L. From human genome to cancer genome: the first decade. Genome Res. 2013 Jul;23(7):1054-62. doi: 10.1101/gr.157602.113. PMID: 23817046; PMCID: PMC3698498.

42. Engeland K. Cell cycle regulation: p53-p21-RB signaling. Cell Death Differ. 2022 May;29(5):946-960. doi: 10.1038/s41418-022-00988-z. Epub 2022 Mar 31. PMID: 35361964; PMCID: PMC9090780.

43. Kalkat M, De Melo J, Hickman KA, Lourenco C, Redel C, Resetca D, Tamachi A, Tu WB, Penn LZ. MYC Deregulation in Primary Human Cancers. Genes (Basel). 2017 May 25;8(6):151. doi: 10.3390/genes8060151. PMID: 28587062; PMCID: PMC5485515

44. Metibemu, D.S., Akinloye, O.A., Akamo, A.J. et al. Exploring receptor tyrosine kinases-inhibitors in Cancer treatments. Egypt J Med Hum Genet 20, 35 (2019). https://doi.org/10.1186/s43042-019-0035-0

45. Chaudhary PK, Kim S. An Insight into GPCR and G-Proteins as Cancer Drivers. Cells. 2021 Nov 24;10(12):3288. doi: 10.3390/cells10123288. PMID: 34943797; PMCID: PMC8699078.

46. Prior IA, Lewis PD, Mattos C. A comprehensive survey of Ras mutations in cancer. Cancer Res. 2012 May 15;72(10):2457-67. doi: 10.1158/0008-5472.CAN-11-2612. PMID: 22589270; PMCID: PMC3354961.

47. Vaidya FU, Sufiyan Chhipa A, Mishra V, Gupta VK, Rawat SG, Kumar A, Pathak C.

Molecular and cellular paradigms of multidrug resistance in cancer. Cancer Rep (Hoboken). 2022 Dec;5(12):e1291. doi: 10.1002/cnr2.1291. Epub 2020 Oct 13. PMID: 33052041; PMCID: PMC9780431.

48. Telkoparan-Akillilar P, Panieri E, Cevik D, Suzen S, Saso L. Therapeutic Targeting of the NRF2 Signaling Pathway in Cancer. Molecules. 2021 Mar 5;26(5):1417. doi: 10.3390/molecules26051417. PMID: 33808001; PMCID: PMC7961421.

49. Hua, H., Kong, Q., Yin, J. et al. Insulin-like growth factor receptor signaling in tumorigenesis and drug resistance: a challenge for cancer therapy. J Hematol Oncol 13, 64 (2020). https://doi.org/10.1186/s13045-020-00904-3

50. Su, Z., Yang, Z., Xu, Y. et al. Apoptosis, autophagy, necroptosis, and cancer metastasis. Mol Cancer 14, 48 (2015). https://doi.org/10.1186/s12943-015-0321-5

51. Kaloni D, Diepstraten ST, Strasser A, Kelly GL. BCL-2 protein family: attractive targets for cancer therapy. Apoptosis. 2022 Nov 7. doi: 10.1007/s10495-022-01780-7. Epub ahead of print. PMID: 36342579.

52. Popova, N.V.; Jücker, M. The Functional Role of Extracellular Matrix Proteins in Cancer. Cancers 2022, 14, 238. https://doi.org/10.3390/cancers14010238

53. Kessler T, Hache H, Wierling C. Integrative analysis of cancer-related signaling pathways. Front Physiol. 2013 Jun 4;4:124. doi: 10.3389/fphys.2013.00124. PMID: 23760067; PMCID: PMC3671203.

54. Hanahan D, Weinberg RA. The hallmarks of cancer. Cell. 2000 Jan 7;100(1):57-70. doi: 10.1016/s0092-8674(00)81683-9. PMID: 10647931.

55. Lee EY, Muller WJ. Oncogenes and tumor suppressor genes. Cold Spring Harb Perspect Biol. 2010 Oct;2(10):a003236. doi: 10.1101/cshperspect.a003236. Epub 2010 Aug 18. PMID: 20719876; PMCID: PMC2944361.

56. Orr B, Compton DA. A double-edged sword: how oncogenes and tumor suppressor genes can contribute to chromosomal instability. Front Oncol. 2013 Jun 27;3:164. doi: 10.3389/fonc.2013.00164. PMID: 23825799; PMCID: PMC3695391.

57. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011 Mar

4;144(5):646-74. doi: 10.1016/j.cell.2011.02.013. PMID: 21376230.

58. Hanahan D. Hallmarks of Cancer: New Dimensions. Cancer Discov. 2022 Jan;12(1):31-46. doi: 10.1158/2159-8290.CD-21-1059. PMID: 35022204.

59. Adjei AA, Hidalgo M. Intracellular signal transduction pathway proteins as targets for cancer therapy. J Clin Oncol. 2005 Aug 10;23(23):5386-403. doi: 10.1200/JCO.2005.23.648. Epub 2005 Jun 27. PMID: 15983388.

60. Bayat Mokhtari R, Homayouni TS, Baluch N, Morgatskaya E, Kumar S, Das B, Yeger H. Combination therapy in combating cancer. Oncotarget. 2017 Jun 6;8(23):38022-38043. doi: 10.18632/oncotarget.16723. PMID: 28410237; PMCID: PMC5514969.

61.Sever R, Brugge JS. Signal transduction in cancer. Cold Spring Harb Perspect Med. 2015 Apr1;5(4):a006098. doi: 10.1101/cshperspect.a006098. PMID: 25833940; PMCID: PMC4382731.

62.Dillon M, Lopez A, Lin E, Sales D, Perets R, Jain P. Progress on Ras/MAPK Signaling Research and Targeting in Blood and Solid Cancers. Cancers. 2021; 13(20):5059. https://doi.org/10.3390/cancers13205059

63. Santarpia L, Lippman SM, El-Naggar AK. Targeting the MAPK-RAS-RAF signaling pathway in cancer therapy. Expert Opin Ther Targets. 2012 Jan;16(1):103-19. doi: 10.1517/14728222.2011.645805. Epub 2012 Jan 12. PMID: 22239440; PMCID: PMC3457779.

64. Hua, H., Kong, Q., Zhang, H. et al. Targeting mTOR for cancer therapy. J Hematol Oncol 12, 71 (2019). https://doi.org/10.1186/s13045-019-0754-1

65. Yang, J., Nie, J., Ma, X. et al. Targeting PI3K in cancer: mechanisms and advances in clinical trials. Mol Cancer 18, 26 (2019). https://doi.org/10.1186/s12943-019-0954-x

66. Papa A, Pandolfi PP. The PTEN⁻PI3K Axis in Cancer. Biomolecules. 2019 Apr 17;9(4):153. doi: 10.3390/biom9040153. PMID: 30999672; PMCID: PMC6523724.

67. Alzahrani AS. PI3K/Akt/mTOR inhibitors in cancer: At the bench and bedside. Semin Cancer Biol. 2019 Dec;59:125-132. doi: 10.1016/j.semcancer.2019.07.009. Epub 2019 Jul 16.

PMID: 31323288.

68. Brooks AJ, Putoczki T. JAK-STAT Signalling Pathway in Cancer. Cancers (Basel). 2020 Jul 20;12(7):1971. doi: 10.3390/cancers12071971. PMID: 32698360; PMCID: PMC7409105.

69. Thomas, S., Snowden, J., Zeidler, M. et al. The role of JAK/STAT signalling in the pathogenesis, prognosis and treatment of solid tumours. Br J Cancer 113, 365–371 (2015). https://doi.org/10.1038/bjc.2015.233

70. Loh CY, Arya A, Naema AF, Wong WF, Sethi G, Looi CY. Signal Transducer and Activator of Transcription (STATs) Proteins in Cancer and Inflammation: Functions and Therapeutic Implication. Front Oncol. 2019 Feb 21;9:48. doi: 10.3389/fonc.2019.00048. PMID: 30847297; PMCID: PMC6393348.

71. Owen KL, Brockwell NK, Parker BS. JAK-STAT Signaling: A Double-Edged Sword of Immune Regulation and Cancer Progression. Cancers (Basel). 2019 Dec 12;11(12):2002. doi: 10.3390/cancers11122002. PMID: 31842362; PMCID: PMC6966445.

72. Rah B, Rather RA, Bhat GR, Baba AB, Mushtaq I, Farooq M, Yousuf T, Dar SB, Parveen S, Hassan R, Mohammad F, Qassim I, Bhat A, Ali S, Zargar MH, Afroze D. JAK/STAT Signaling: Molecular Targets, Therapeutic Opportunities, and Limitations of Targeted Inhibitions in Solid Malignancies. Front Pharmacol. 2022 Mar 24;13:821344. doi: 10.3389/fphar.2022.821344. PMID: 35401182; PMCID: PMC8987160.

73. Zhao M, Mishra L, Deng CX. The role of TGF-β/SMAD4 signaling in cancer. Int J Biol Sci. 2018 Jan 12;14(2):111-123. doi: 10.7150/ijbs.23230. PMID: 29483830; PMCID: PMC5821033.

74. Samanta D, Datta PK. Alterations in the Smad pathway in human cancers. Front Biosci (Landmark Ed). 2012 Jan 1;17(4):1281-93. doi: 10.2741/3986. PMID: 22201803; PMCID: PMC4281477.

75. Akhurst RJ. Targeting TGF-β Signaling for Therapeutic Gain. Cold Spring Harb Perspect Biol. 2017 Oct 3;9(10):a022301. doi: 10.1101/cshperspect.a022301. PMID: 28246179; PMCID: PMC5630004.

76. Huang CY, Chung CL, Hu TH, Chen JJ, Liu PF, Chen CL. Recent progress in TGF-β inhibitors for cancer therapy. Biomed Pharmacother. 2021 Feb;134:111046. doi: 10.1016/j.biopha.2020.111046. Epub 2020 Dec 16. PMID: 33341049.

77. Han, Y. Analysis of the role of the Hippo pathway in cancer. J Transl Med 17, 116 (2019). https://doi.org/10.1186/s12967-019-1869-4

78. Cunningham R, Hansen CG. The Hippo pathway in cancer: YAP/TAZ and TEAD as therapeutic targets in cancer. Clin Sci (Lond). 2022 Feb 11;136(3):197-222. doi: 10.1042/CS20201474. PMID: 35119068; PMCID: PMC8819670.

79. Calses PC, Crawford JJ, Lill JR, Dey A. Hippo Pathway in Cancer: Aberrant Regulation and Therapeutic Opportunities. Trends Cancer. 2019 May;5(5):297-307. doi:10.1016/j.trecan.2019.04.001. Epub 2019 May 16. PMID: 31174842.

80. Zhan, T., Rindtorff, N. & Boutros, M. Wnt signaling in cancer. Oncogene 36, 1461–1473 (2017). https://doi.org/10.1038/onc.2016.304

81. Martin-Orozco E, Sanchez-Fernandez A, Ortiz-Parra I, Ayala-San Nicolas M. WNT Signaling in Tumors: The Way to Evade Drugs and Immunity. Front Immunol. 2019 Dec 20;10:2854. doi: 10.3389/fimmu.2019.02854. PMID: 31921125; PMCID: PMC6934036.

82. Zhang, Y., Wang, X. Targeting the Wnt/β-catenin signaling pathway in cancer. J Hematol Oncol 13, 165 (2020). https://doi.org/10.1186/s13045-020-00990-3

83. Skoda AM, Simovic D, Karin V, Kardum V, Vranic S, Serman L. The role of the Hedgehog signaling pathway in cancer: A comprehensive review. Bosn J Basic Med Sci. 2018 Feb 20;18(1):8-20. doi: 10.17305/bjbms.2018.2756. PMID: 29274272; PMCID: PMC5826678.

84. Kumar V, Vashishta M, Kong L, Wu X, Lu JJ, Guha C, Dwarakanath BS. The Role of Notch, Hedgehog, and Wnt Signaling Pathways in the Resistance of Tumors to Anticancer Therapies. Front Cell Dev Biol. 2021 Apr 22;9:650772. doi: 10.3389/fcell.2021.650772. PMID: 33968932; PMCID: PMC8100510.

85. Chang, W.H., Lai, A.G. Aberrations in Notch-Hedgehog signalling reveal cancer stem cells harbouring conserved oncogenic properties associated with hypoxia and immunoevasion. Br J

Cancer 121, 666–678 (2019). https://doi.org/10.1038/s41416-019-0572-9

86. Shibata M, Hoque MO. Targeting Cancer Stem Cells: A Strategy for Effective Eradication of Cancer. Cancers. 2019; 11(5):732. https://doi.org/10.3390/cancers11050732

87. Yang, L., Shi, P., Zhao, G. et al. Targeting cancer stem cell pathways for cancer therapy. Sig Transduct Target Ther 5, 8 (2020). https://doi.org/10.1038/s41392-020-0110-5

88. Shih, VS., Tsui, R., Caldwell, A. et al. A single NFκB system for both canonical and non-canonical signaling. Cell Res 21, 86–102 (2011). https://doi.org/10.1038/cr.2010.161

89. Hoesel, B., Schmid, J.A. The complexity of NF-κB signaling in inflammation and cancer. Mol Cancer 12, 86 (2013). https://doi.org/10.1186/1476-4598-12-86

90. Huber MA, Beug H, Wirth T. Epithelial-mesenchymal transition: NF-kappaB takes center stage. Cell Cycle. 2004 Dec;3(12):1477-80. doi: 10.4161/cc.3.12.1280. Epub 2004 Dec 4. PMID: 15539952.

91. Fonseca LC, Dadarkar SS, Lobo AS, Mishra PB, Thakkar AD, Chandrababu S, Padigaru M. NF-κB-mediated anti-inflammatory activity of the sesquiterpene lactone 7-hydroxyfrullanolide. Eur J Pharmacol. 2011 Apr 25;657(1-3):41-50. doi: 10.1016/j.ejphar.2011.01.050. Epub 2011 Feb 4. PMID: 21296061.

92. Oeckinghaus, A., Hayden, M. & Ghosh, S. Crosstalk in NF-κB signaling pathways. Nat Immunol 12, 695–708 (2011). https://doi.org/10.1038/ni.2065

93. Luo JL, Kamata H, Karin M. IKK/NF-kappaB signaling: balancing life and death--a new approach to cancer therapy. J Clin Invest. 2005 Oct;115(10):2625-32. doi: 10.1172/JCI26322. PMID: 16200195; PMCID: PMC1236696.

94. Erstad DJ, Cusack JC Jr. Targeting the NF-κB pathway in cancer therapy. Surg Oncol Clin N Am. 2013 Oct;22(4):705-46. doi: 10.1016/j.soc.2013.06.011. Epub 2013 Aug 6. PMID: 24012396.

95. Hoong BYD, Gan YH, Liu H, Chen ES. cGAS-STING pathway in oncogenesis and cancer therapeutics. Oncotarget. 2020 Jul 28;11(30):2930-2955. doi: 10.18632/oncotarget.27673. PMID: 32774773; PMCID: PMC7392626.

96. Khoo LT, Chen LY. Role of the cGAS-STING pathway in cancer development and oncotherapeutic approaches. EMBO Rep. 2018 Dec;19(12):e46935. doi: 10.15252/embr.201846935. Epub 2018 Nov 16. PMID: 30446584; PMCID: PMC6280650.

97. Jiang, M., Chen, P., Wang, L. et al. cGAS-STING, an important pathway in cancer immunotherapy. J Hematol Oncol 13, 81 (2020). https://doi.org/10.1186/s13045-020-00916-z

98. Kümper S, Mardakheh FK, McCarthy A, Yeo M, Stamp GW, Paul A, Worboys J, Sadok A, Jørgensen C, Guichard S, Marshall CJ. Rho-associated kinase (ROCK) function is essential for cell cycle progression, senescence and tumorigenesis. Elife. 2016 Jan 14;5:e12994. doi: 10.7554/eLife.12203. PMID: 26765561; PMCID: PMC4798951.

99. Kim S, Kim SA, Han J, Kim IS. Rho-Kinase as a Target for Cancer Therapy and Its Immunotherapeutic Potential. Int J Mol Sci. 2021 Nov 29;22(23):12916. doi: 10.3390/ijms222312916. PMID: 34884721; PMCID: PMC8657458.

100. Ohashi H, Hasegawa M, Wakimoto K, Miyamoto-Sato E. Next-generation technologies for multiomics approaches including interactome sequencing. Biomed Res Int. 2015;2015:104209. doi: 10.1155/2015/104209. Epub 2015 Jan 12. PMID: 25649523; PMCID: PMC4306365.

101. Heo YJ, Hwa C, Lee GH, Park JM, An JY. Integrative Multi-Omics Approaches in Cancer Research: From Biological Networks to Clinical Subtypes. Mol Cells. 2021 Jul 31;44(7):433-443. doi: 10.14348/molcells.2021.0042. PMID: 34238766; PMCID: PMC8334347.

102. Ding MQ, Chen L, Cooper GF, Young JD, Lu X. Precision Oncology beyond Targeted Therapy: Combining Omics Data with Machine Learning Matches the Majority of Cancer Cells to Effective Therapeutics. Mol Cancer Res. 2018 Feb;16(2):269-278. doi: 10.1158/1541-7786.MCR-17-0378. Epub 2017 Nov 13. PMID: 29133589; PMCID: PMC5821274.

103. Nicora G, Vitali F, Dagliati A, Geifman N, Bellazzi R. Integrated Multi-Omics Analyses in Oncology: A Review of Machine Learning Methods and Tools. Front Oncol. 2020 Jun 30;10:1030. doi: 10.3389/fonc.2020.01030. PMID: 32695678; PMCID: PMC7338582.

104. Erickson BJ. Basic Artificial Intelligence Techniques: Machine Learning and Deep

Learning. Radiologic Clinics of North America. 2021 Nov;59(6):933-940. DOI: 10.1016/j.rcl.2021.06.004. PMID: 34689878.

105. Lee, DonHee, and Seong No Yoon. 2021. "Application of Artificial Intelligence-Based Technologies in the Healthcare Industry: Opportunities and Challenges" International Journal of Environmental Research and Public Health 18, no. 1: 271. https://doi.org/10.3390/ijerph18010271

106. Filipp, F.V. Opportunities for Artificial Intelligence in Advancing Precision Medicine. Curr Genet Med Rep 7, 208–213 (2019). https://doi.org/10.1007/s40142-019-00177-4

107. Azuaje, F. Artificial intelligence for precision oncology: beyond patient stratification. npj Precision Onc 3, 6 (2019). https://doi.org/10.1038/s41698-019-0078-1

108. Deng C, Ji X, Rainey C, Zhang J, Lu W. Integrating Machine Learning with Human Knowledge. iScience. 2020 Oct 9;23(11):101656. doi: 10.1016/j.isci.2020.101656. PMID: 33134890; PMCID: PMC7588855.

109. Shimizu H, Nakayama KI. Artificial intelligence in oncology. Cancer Sci. 2020 May;111(5):1452-1460. doi: 10.1111/cas.14377. Epub 2020 Mar 21. PMID: 32133724; PMCID: PMC7226189.

110. Adam, G., Rampášek, L., Safikhani, Z. et al. Machine learning approaches to drug response prediction: challenges and recent progress. npj Precis. Onc. 4, 19 (2020).

111. Kuenzi BM, Park J, Fong SH, Sanchez KS, Lee J, Kreisberg JF, Ma J, Ideker T. Predicting Drug Response and Synergy Using a Deep Learning Model of Human Cancer Cells. Cancer Cell. 2020 Nov 9;38(5):672-684.e6. doi: 10.1016/j.ccell.2020.09.014. Epub 2020 Oct 22. PMID: 33096023; PMCID: PMC7737474.

112. Jumper, J., Evans, R., Pritzel, A. et al. Highly accurate protein structure prediction with AlphaFold. Nature 596, 583–589 (2021). https://doi.org/10.1038/s41586-021-03819-2

113. Thornton, J.M., Laskowski, R.A. & Borkakoti, N. AlphaFold heralds a data-driven revolution in biology and medicine. Nat Med 27, 1666–1669 (2021). https://doi.org/10.1038/s41591-021-01533-0

114. Bera K, Schalper KA, Rimm DL, Velcheti V, Madabhushi A. Artificial intelligence in

digital pathology - new tools for diagnosis and precision oncology. Nat Rev Clin Oncol. 2019 Nov;16(11):703-715. doi: 10.1038/s41571-019-0252-y. Epub 2019 Aug 9. PMID: 31399699; PMCID: PMC6880861.
115. Cancer Genome Atlas Research Network, Weinstein JN, Collisson EA, Mills GB, Shaw KR, Ozenberger BA, Ellrott K, Shmulevich I, Sander C, Stuart JM. The Cancer Genome Atlas Pan-Cancer analysis project. Nat Genet. 2013 Oct;45(10):1113-20. doi: 10.1038/ng.2764. PMID: 24071849; PMCID: PMC3919969.

116. Tomczak K, Czerwińska P, Wiznerowicz M. The Cancer Genome Atlas (TCGA): an immeasurable source of knowledge. Contemp Oncol (Pozn). 2015;19(1A):A68-77. doi: 10.5114/wo.2014.47136. PMID: 25691825; PMCID: PMC4322527.

117. Chakravarty D, Gao J, Phillips SM, Kundra R, Zhang H, Wang J, Rudolph JE, Yaeger R, Soumerai T, Nissan MH, Chang MT, Chandarlapaty S, Traina TA, Paik PK, Ho AL, Hantash FM, Grupe A, Baxi SS, Callahan MK, Snyder A, Chi P, Danila D, Gounder M, Harding JJ, Hellmann MD, Iyer G, Janjigian Y, Kaley T, Levine DA, Lowery M, Omuro A, Postow MA, Rathkopf D, Shoushtari AN, Shukla N, Voss M, Paraiso E, Zehir A, Berger MF, Taylor BS, Saltz LB, Riely GJ, Ladanyi M, Hyman DM, Baselga J, Sabbatini P, Solit DB, Schultz N. OncoKB: A Precision Oncology Knowledge Base. JCO Precis Oncol. 2017 Jul;2017:PO.17.00011. doi: 10.1200/PO.17.00011. Epub 2017 May 16. PMID: 28890946; PMCID: PMC5586540.

118. Pallarz S, Benary M, Lamping M, Rieke D, Starlinger J, Sers C, Wiegandt DL, Seibert M, Ševa J, Schäfer R, Keilholz U, Leser U. Comparative Analysis of Public Knowledge Bases for Precision Oncology. JCO Precis Oncol. 2019 Jul 24;3:PO.18.00371. doi: 10.1200/PO.18.00371. PMID: 32914021; PMCID: PMC7446431.

119. Chandran UR, Medvedeva OP, Barmada MM, Blood PD, Chakka A, Luthra S, Ferreira A, Wong KF, Lee AV, Zhang Z, Budden R, Scott JR, Berndt A, Berg JM, Jacobson RS. TCGA Expedition: A Data Acquisition and Management System for TCGA Data. PLoS One. 2016 Oct 27;11(10):e0165395. doi: 10.1371/journal.pone.0165395. PMID: 27788220; PMCID: PMC5082933.

120. Tatlow, P., Piccolo, S. A cloud-based workflow to quantify transcript-expression levels in public cancer compendia. Sci Rep 6, 39259 (2016). https://doi.org/10.1038/srep39259

121. Li, Y., Kang, K., Krahn, J.M. et al. A comprehensive genomic pan-cancer classification using The Cancer Genome Atlas gene expression data. BMC Genomics 18, 508 (2017). https://doi.org/10.1186/s12864-017-3906-0

122. Cooper LA, Demicco EG, Saltz JH, Powell RT, Rao A, Lazar AJ. PanCancer insights from The Cancer Genome Atlas: the pathologist's perspective. J Pathol. 2018 Apr;244(5):512-524. doi: 10.1002/path.5028. Epub 2018 Feb 22. PMID: 29288495; PMCID: PMC6240356.
123. Hoadley KA, Yau C, Wolf DM, Cherniack AD, Tamborero D, Ng S, Leiserson MDM, Niu B, McLellan MD, Uzunangelov V, Zhang J, Kandoth C, Akbani R, Shen H, Omberg L, Chu A, Margolin AA, Van't Veer LJ, Lopez-Bigas N, Laird PW, Raphael BJ, Ding L, Robertson AG, Byers LA, Mills GB, Weinstein JN, Van Waes C, Chen Z, Collisson EA; Cancer Genome Atlas Research Network, Benz CC, Perou CM, Stuart JM. Multiplatform analysis of 12 cancer types reveals molecular classification within and across tissues of origin. Cell. 2014 Aug 14;158(4):929-944. doi: 10.1016/j.cell.2014.06.049. Epub 2014 Aug 7. PMID: 25109877; PMCID: PMC4152462.

124. Hoadley KA, Yau C, Hinoue T, Wolf DM, Lazar AJ, Drill E, Shen R, Taylor AM, Cherniack AD, Thorsson V, Akbani R, Bowlby R, Wong CK, Wiznerowicz M, Sanchez-Vega F, Robertson AG, Schneider BG, Lawrence MS, Noushmehr H, Malta TM; Cancer Genome Atlas Network, Stuart JM, Benz CC, Laird PW. Cell-of-Origin Patterns Dominate the Molecular Classification of 10,000 Tumors from 33 Types of Cancer. Cell. 2018 Apr 5;173(2):291-304.e6. doi: 10.1016/j.cell.2018.03.022. PMID: 29625048; PMCID: PMC5957518.

125. Sanchez-Vega F, Mina M, Armenia J, Chatila WK, Luna A, La KC, Dimitriadoy S, Liu DL, Kantheti HS, Saghafinia S, Chakravarty D, Daian F, Gao Q, Bailey MH, Liang WW, Foltz SM, Shmulevich I, Ding L, Heins Z, Ochoa A, Gross B, Gao J, Zhang H, Kundra R, Kandoth C, Bahceci I, Dervishi L, Dogrusoz U, Zhou W, Shen H, Laird PW, Way GP, Greene CS, Liang H, Xiao Y, Wang C, Iavarone A, Berger AH, Bivona TG, Lazar AJ, Hammer GD, Giordano T, Kwong LN, McArthur G, Huang C, Tward AD, Frederick MJ, McCormick F, Meyerson M; Cancer Genome Atlas Research Network, Van Allen EM, Cherniack AD, Ciriello G, Sander C, Schultz N. Oncogenic Signaling Pathways in The Cancer Genome Atlas. Cell. 2018 Apr 5;173(2):321-337.e10. doi: 10.1016/j.cell.2018.03.035. PMID: 29625050; PMCID: PMC6070353.

126. Wang E, Zaman N, Mcgee S, Milanese JS, Masoudi-Nejad A, O'Connor-McCourt M. Predictive genomics: a cancer hallmark network framework for predicting tumor clinical phenotypes using genome sequencing data. Semin Cancer Biol. 2015 Feb;30:4-12. doi: 10.1016/j.semcancer.2014.04.002. Epub 2014 Apr 18. PMID: 24747696.

127. Wang E. Understanding genomic alterations in cancer genomes using an integrative network approach. Cancer Lett. 2013 Nov 1;340(2):261-9. doi: 10.1016/j.canlet.2012.11.050. Epub 2012 Dec 22. PMID: 23266571.

128. Krogan NJ, Lippman S, Agard DA, Ashworth A, Ideker T. The cancer cell map initiative: defining the hallmark networks of cancer. Mol Cell. 2015 May 21;58(4):690-8. doi:

10.1016/j.molcel.2015.05.008. PMID: 26000852; PMCID: PMC5359018.

129. Ghandi M, Huang FW, Jané-Valbuena J, Kryukov GV, Lo CC, McDonald ER 3rd, Barretina J, Gelfand ET, Bielski CM, Li H, Hu K, Andreev-Drakhlin AY, Kim J, Hess JM, Haas BJ, Aguet F, Weir BA, Rothberg MV, Paolella BR, Lawrence MS, Akbani R, Lu Y, Tiv HL, Gokhale PC, de Weck A, Mansour AA, Oh C, Shih J, Hadi K, Rosen Y, Bistline J, Venkatesan K, Reddy A, Sonkin D, Liu M, Lehar J, Korn JM, Porter DA, Jones MD, Golji J, Caponigro G, Taylor JE, Dunning CM, Creech AL, Warren AC, McFarland JM, Zamanighomi M, Kauffmann A, Stransky N, Imielinski M, Maruvka YE, Cherniack AD, Tsherniak A, Vazquez F, Jaffe JD, Lane AA, Weinstock DM, Johannessen CM, Morrissey MP, Stegmeier F, Schlegel R, Hahn WC, Getz G, Mills GB, Boehm JS, Golub TR, Garraway LA, Sellers WR. Next-generation characterization of the Cancer Cell Line Encyclopedia. Nature. 2019 May;569(7757):503-508. doi: 10.1038/s41586-019-1186-3. Epub 2019 May 8. PMID: 31068700; PMCID: PMC6697103.

130. Junker JP, van Oudenaarden A. Every cell is special: genome-wide studies add a new dimension to single-cell biology. Cell. 2014 Mar 27;157(1):8-11. doi: 10.1016/j.cell.2014.02.010. PMID: 24679522.

131. Reddy RB, Khora SS, Suresh A. Molecular prognosticators in clinically and pathologically distinct cohorts of head and neck squamous cell carcinoma-A meta-analysis approach. PLoS One. 2019 Jul 16;14(7):e0218989. doi: 10.1371/journal.pone.0218989. PMID: 31310629; PMCID: PMC6634788.

132. Saadatpour A, Lai S, Guo G, Yuan GC. Single-Cell Analysis in Cancer Genomics. Trends Genet. 2015 Oct;31(10):576-586. doi: 10.1016/j.tig.2015.07.003. PMID: 26450340; PMCID: PMC5282606.

133. Lim, ZF., Ma, P.C. Emerging insights of tumor heterogeneity and drug resistance mechanisms in lung cancer targeted therapy. J Hematol Oncol 12, 134 (2019). https://doi.org/10.1186/s13045-019-0818-2

134. Dagogo-Jack, I., Shaw, A. Tumour heterogeneity and resistance to cancer therapies. Nat Rev Clin Oncol 15, 81–94 (2018). https://doi.org/10.1038/nrclinonc.2017.166

135. Hong, T.H., Park, WY. Single-cell genomics technology: perspectives. Exp Mol Med 52, 1407–1408 (2020). https://doi.org/10.1038/s12276-020-00495-6

136. Hu P, Zhang W, Xin H, Deng G. Single Cell Isolation and Analysis. Front Cell Dev Biol. 2016 Oct 25;4:116. doi: 10.3389/fcell.2016.00116. PMID: 27826548; PMCID: PMC5078503.

137. Yang Y, Xu J, Ge S, Lai L. CRISPR/Cas: Advances, Limitations, and Applications for Precision Cancer Research. Front Med (Lausanne). 2021 Mar 3;8:649896. doi: 10.3389/fmed.2021.649896. PMID: 33748164; PMCID: PMC7965951.

138. Di Palma S, Bodenmiller B. Unraveling cell populations in tumors by single-cell mass cytometry. Curr Opin Biotechnol. 2015 Feb;31:122-9. doi: 10.1016/j.copbio.2014.07.004. Epub 2014 Aug 11. PMID: 25123841.

139. Guo M, Peng Y, Gao A, Du C, Herman JG. Epigenetic heterogeneity in cancer. Biomark Res. 2019 Oct 31;7:23. doi: 10.1186/s40364-019-0174-y. PMID: 31695915; PMCID: PMC6824025.

140. Yuan Y. Spatial Heterogeneity in the Tumor Microenvironment. Cold Spring Harb Perspect Med. 2016 Aug 1;6(8):a026583. doi: 10.1101/cshperspect.a026583. PMID: 27481837; PMCID: PMC4968167.

141. Brady, L., Kriner, M., Coleman, I. et al. Inter- and intra-tumor heterogeneity of metastatic prostate cancer determined by digital spatial gene expression profiling. Nat Commun 12, 1426 (2021). https://doi.org/10.1038/s41467-021-21615-4

142. Levy-Jurgenson, A., Tekpli, X., Kristensen, V.N. et al. Spatial transcriptomics inferred from pathology whole-slide images links tumor heterogeneity to survival in breast and lung cancer. Sci Rep 10, 18802 (2020). https://doi.org/10.1038/s41598-020-75708-z

143. Ye F, Huang W, Guo G. Studying hematopoiesis using single-cell technologies. J Hematol Oncol. 2017 Jan 21;10(1):27. doi: 10.1186/s13045-017-0401-7. PMID: 28109325; PMCID: PMC5251333.

144. Zheng, B., Fang, L. Spatially resolved transcriptomics provide a new method for cancer research. J Exp Clin Cancer Res 41, 179 (2022). https://doi.org/10.1186/s13046-022-02385-3

145. Xu, Y., Su, GH., Ma, D. et al. Technological advances in cancer immunity: from immunogenomics to single-cell analysis and artificial intelligence. Sig Transduct Target Ther 6, 312 (2021). https://doi.org/10.1038/s41392-021-00729-7

146. Liotta L, Petricoin E. Molecular profiling of human cancer. Nat Rev Genet. 2000 Oct;1(1):48-56. doi: 10.1038/35049567. PMID: 11262874.

147. Karagiannakos A, Adamaki M, Tsintarakis A, Vojtesek B, Fåhraeus R, Zoumpourlis V, Karakostis K. Targeting Oncogenic Pathways in the Era of Personalized Oncology: A Systemic Analysis Reveals Highly Mutated Signaling Pathways in Cancer Patients and Potential Therapeutic Targets. Cancers (Basel). 2022 Jan 28;14(3):664. doi: 10.3390/cancers14030664. PMID: 35158934; PMCID: PMC8833388.

148. Te Beek ET, Teunissen JJM, Postema JWA, Lafeber A, Ten Broek MRJ. Precision medicine and theranostics using radiopharmaceuticals in oncology. Br J Clin Pharmacol. 2022 Jan;88(1):359-361. doi: 10.1111/bcp.14942. Epub 2021 Jun 22. PMID: 34159632.

149. Zahavi D, Weiner L. Monoclonal Antibodies in Cancer Therapy. Antibodies (Basel). 2020 Jul 20;9(3):34. doi: 10.3390/antib9030034. PMID: 32698317; PMCID: PMC7551545.

150. Lord CJ, Ashworth A. PARP inhibitors: Synthetic lethality in the clinic. Science. 2017 Mar 17;355(6330):1152-1158. doi: 10.1126/science.aam7344. Epub 2017 Mar 16. PMID: 28302823; PMCID: PMC6175050.

151. Slade D. PARP and PARG inhibitors in cancer treatment. Genes Dev. 2020 Mar 1;34(5-6):360-394. doi: 10.1101/gad.334516.119. Epub 2020 Feb 6. PMID: 32029455; PMCID: PMC7050487.

152. Rossi JF, Céballos P, Lu ZY. Immune precision medicine for cancer: a novel insight based on the efficiency of immune effector cells. Cancer Commun (Lond). 2019 Jun 14;39(1):34. doi: 10.1186/s40880-019-0379-3. PMID: 31200766; PMCID: PMC6567551.

153. Pfohl, U.; Pflaume, A.; Regenbrecht, M.; Finkler, S.; Graf Adelmann, Q.; Reinhard, C.; Regenbrecht, C.R.A.; Wedeken, L. Precision Oncology Beyond Genomics: The Future Is Here—It Is Just Not Evenly Distributed. Cells 2021, 10, 928. https://doi.org/10.3390/cells10040928

154. Baghban, R., Roshangar, L., Jahanban-Esfahlan, R. et al. Tumor microenvironment complexity and therapeutic implications at a glance. Cell Commun Signal 18, 59 (2020). https://doi.org/10.1186/s12964-020-0530-4

155. Kareva I. A Combination of Immune Checkpoint Inhibition with Metronomic Chemotherapy as a Way of Targeting Therapy-Resistant Cancer Cells. International Journal of

Molecular Sciences. 2017; 18(10):2134. https://doi.org/10.3390/ijms18102134

156. Chen G, Bodogai M, Tamehiro N, Shen C, Dou J. Cancer Immunotherapy: Theory and Application. J Immunol Res. 2018 Jun 21;2018:7502161. doi: 10.1155/2018/7502161. PMID: 30035133; PMCID: PMC6033242.

157. Kiyotani K, Toyoshima Y, Nakamura Y. Personalized immunotherapy in cancer precision medicine. Cancer Biol Med. 2021 Aug 9;18(4):955–65. doi: 10.20892/j.issn.2095-3941.2021.0032. Epub ahead of print. PMID: 34369137; PMCID: PMC8610159.

158. Zhao, B.; Chen, S.; Hong, Y.; Jia, L.; Zhou, Y.; He, X.; Wang, Y.; Tian, Z.; Yang, Z.; Gao, D. Research Progress of Conjugated Nanomedicine for Cancer Treatment. Pharmaceutics 2022,14, 1522. https://doi.org/10.3390/pharmaceutics14071522

159. Yao Y, Zhou Y, Liu L, Xu Y, Chen Q, Wang Y, Wu S, Deng Y, Zhang J, Shao A. Nanoparticle-Based Drug Delivery in Cancer Therapy and Its Role in Overcoming Drug Resistance. Front Mol Biosci. 2020 Aug 20;7:193. doi: 10.3389/fmolb.2020.00193. PMID: 32974385; PMCID: PMC7468194.

160. Dupont CA, Riegel K, Pompaiah M, Juhl H, Rajalingam K. Druggable genome and precision medicine in cancer: current challenges. FEBS J. 2021 Nov;288(21):6142-6158. doi: 10.1111/febs.15788. Epub 2021 Mar 19. PMID: 33626231.

161. Pereira M.A. et al. (2020). Cancer Genomics in Precision Oncology: Applications, Challenges, and Prospects. In: Masood, N., Shakil Malik, S. (eds) 'Essentials of Cancer Genomic, Computational Approaches and Precision Medicine. Springer, Singapore. https://doi.org/10.1007/978-981-15-1067-0_21

162. Pantziarka P, Bouche G, André N. "Hard" Drug Repurposing for Precision Oncology: The Missing Link? Front Pharmacol. 2018 Jun 14;9:637. doi: 10.3389/fphar.2018.00637. PMID: 29962954; PMCID: PMC6010551.

163. Oprea TI, Bauman JE, Bologa CG, Buranda T, Chigaev A, Edwards BS, Jarvik JW, Gresham HD, Haynes MK, Hjelle B, Hromas R, Hudson L, Mackenzie DA, Muller CY, Reed JC, Simons PC, Smagley Y, Strouse J, Surviladze Z, Thompson T, Ursu O, Waller A, Wandinger-Ness A, Winter SS, Wu Y, Young SM, Larson RS, Willman C, Sklar LA. Drug Repurposing from an Academic Perspective. Drug Discov Today, Ther Strateg. 2011 Winter;8(3-4):61-69. doi: 10.1016/j.ddstr.2011.10.002. PMID: 22368688; PMCID: PMC3285382.

164. Yip HYK, Papa A. Signaling Pathways in Cancer: Therapeutic Targets, Combinatorial Treatments, and New Developments. Cells. 2021 Mar 16;10(3):659. doi: 10.3390/cells10030659. PMID: 33809714; PMCID: PMC8002322.

165. Dugger SA, Platt A, Goldstein DB. Drug development in the era of precision medicine. Nat Rev Drug Discov. 2018 Mar;17(3):183-196. doi: 10.1038/nrd.2017.226. Epub 2017 Dec 8. PMID: 29217837; PMCID: PMC6287751.

Supplementary File 1: New FDA-Approved Oncology Drugs (2021–2022) (https://ascopost.com/issues/june-3-2022-narratives-special-issue/new-fda-approved-oncology-drugs-2021-2022/#.ZDUJRrQ2lAE.)

Supplementary File 2: Ongoing/Cancer Accelerated Approvals (https://www.fda.gov/drugs/resources-information-approved-drugs/ongoing-cancer-accelerated- approvals)

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

---

Manish Kumar

School of Bio Sciences & Technology

Vellore Institute of Technology, Vellore, Tamil Nadu, India

Emails: kmanish125@yahoo.com, kmanish.bt125@gmail.com

ORCID: https://orcid.org/0000-0002-6021-7063

CORRESPONDENCE

1.

C/O. Sri M. Narayan Swami

7/1A, 1st Street, Bhavani Nagar

Katpadi P.O. Dharapadavedu,

Vellore- 632007, Tamil Nadu, India

2.

ME-010-0017, Dhruvneeti Colony

Near Samarpan Hospital, Rajneeti Road

Madhopur, P.0. Basudeopur

Munger- 811202, Bihar, India

Abstract: Cancer is a complex disease having a number of composite problems to be considered including cancer immune evasion, therapy resistance, and recurrence for a cure. Fundamentally, it remains a genetic disease as diverse aspects of the complexity of tumor growth and cancer development relate to its genetic machinery and require addressing the problems at the level of genome and epigenome. Importantly, patients with the same cancer types respond differently to cancer therapies indicating the need for patient-specific treatment options. Precision oncology is a form of cancer therapy that focuses on the genetic profiling of tumors to identify molecular alterations involved in cancer development for custom-tailored personalized treatment of the deadly disease. This article aims to briefly explain the foundations and frontiers of precision oncology in the context of ongoing technological advances in this regard to assess its scope and importance in the realization of a proper cure for cancer.

Keywords: Gene Mutation; Cancer Genomics; p53; K-Ras; C-Myc; Bcl-2, Cancer Stem Cells; Targeted Therapy; Immunotherapy, Precision Medicine.

1. Introduction

Cancer is a devastating disease causing one in six deaths globally with a huge physical, psychological, and economic impact on people affected by the disease. It continues to be the second most common cause of hospital deaths after heart disease, most of which can be prevented by an early diagnosis and improving prevention and treatment strategies for the disease. It requires an efficient diagnosis of cancer, the development of efficacious treatment options, and a better understanding of the socioeconomic factors that affect cancer incidence, prevalence, and related deaths across the globe [1,2]. More than 100 cancer types with sub-types have been determined based on location, cell of origin, and genetic variations that influence cancer development 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 also develop frequently in hematopoietic tissues such as leukemia and lymphomaand in the nervous tissues, e.g., gliomas, and neuroblastomas. They are among the most commoncancer types taking a high toll in terms of lives and property throughout the world [3,4]. Thus, considering the vast number of cancer incidences worldwide, a formal initiative towards fightingthe menace of cancer was needed which first appeared in the United States as the National Cancer Act of 1971 signed by President Richard Nixon, for promoting cancer research and application of the outcomes for minimizing cancer incidences and mortality rates associated withthe disease. The act was euphemistically described as the "War on Cancer", and 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 the treatment, cure, and eradication of cancer [5]. A similar approach was adopted by most other developed and developing nations in the following years to combat the deadly disease which has succeeded in satisfying the purpose involved to a good extent since then despite the fact, as feared and as evidence suggests, that demographic factors played a role in cancer development [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 the rapid advances realized in clinical oncology over the years. [8.9]. However, the fight against cancer is far from over as an estimation by the WHO in 2018 revealed that cancer incidence would be doubled to

approximately 37 million new cases by 2040 with no confirmed remedy for most cancer types in the sight [10,11]. While researchers continue the endeavors to identify the exact causes of different 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 therapy available for cancer for quite some time such as chemotherapy, immunotherapy, hormonal therapy, targeted drug therapy, radiation therapy, surgery, stem cell transplant, etc. One can receive a single type of treatment or a combination of therapies, but whatever the treatment regimen, it must bring the much-needed cure that remains largely elusive till now [12].

Rigorous cancer research in the past few decades supported by advances in cell and molecularbiology has led scientists to clearly understand there are genetic changes associated with cancer incidences that cause the disease to grow and spread to other parts of the body. Cancer is initiated as the result of uncontrolled cell division and proliferation leading to tumor formation which culminates in metastasis that involves the dissemination of tumor cells to new sites in the body forming secondary tumors, and is responsible for about 90% of cancer-related deaths in reality. Cell proliferation requires a balanced rate of cell growth and division to maintain the increase in cell numbers for growth and development, maintenance of tissue homoeostasis and wound healing. The fundamental abnormality leading to cancer development is unwanted cell proliferation due to an absence of balance between cell divisions and cell loss through cell death and differentiation. The division relies on cell cycle regulation that generally involves extracellular growth-regulatory signals as well as internal signaling proteins monitoring the genetic integrity of the cell to ascertain that cellular developments go well in time. It 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 in the transformed cells of the tumor and other cellular activities accompanying cancer progression such as angiogenesis, invasion and metastasis are mainly guided by changes in the concerned genes, and the factors that cause these genetic changes often tend to provoke cancerous development [13,14]. Every single gene in the body is likely to have received deleterious changes in its DNA sequence, i.e., mutations on a number of occasions in the cell's lifetime while the repair mechanism in place would restrict the noticeable changes. In this way, the generation of cancer must be conclusively linked to the sustained gene mutations caused by some external agents called mutagens that often lead to the appearance of different somatic variants or certain changes that might have been inherited in the body. Importantly, a single mutation will not be enough to transform a normal cell into a cancer cell as it would require a number of changes to accumulate in the cells in the course of time for cancerous development to take place. For example, 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 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 ordinarily be required for cancer manifestation to take place and so it must 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. 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 [16]. It is observed because of some physical modificationsin chromatin structure capable of influencing the pattern of gene expression often led by DNA methylation, histone modifications, and miRNA-based alterations inside the cell. Epigenetic regulations of DNA and RNA usually control how genes are turned on or off, and so play important roles in maintaining normal cell behavior whose deregulation causes alterations in gene expression patterns to potentially influence tumorigenesis. The changes are frequently accompanied 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. Although epigenetic changes will not alter the sequence of DNA, 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 may is not the whole regarding 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. Thus, the genome and the epigenome could regulate the progression of cancer through mutations. Interferences between the two are therefore anticipated and can be exploited to provide new possibilities for cancer treatment [17].

Cancer in general remains a multi-step process triggered by mutations leading to the activation of specific oncogenic pathways with the concurrent inactivation of tumor suppressor genes that act as sentinels to control unwanted cell growth and proliferation. Scientists have been trying to analyze the totality of cancer-causing gene mutations regarded as the “mutational landscape’, of different types of cancer types and to target them effectively for cancer cure. Most of these biochemical processes are conserved in model organisms such as the free-living transparent nematode Caenorhabditis elegans and the fruit fly Drosophila melanogaster alongsidemice and other large animal models, and are widely used due to the ease of their genetic manipulation to study the complex biology of cancer. The somatic cell mutations, called 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 [18]. 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 are sure to 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 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 reveal 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. Cancer whole-genome sequencing (WGS) remains the most comprehensive method for identifying variants in non-coding regions as targeted approaches like exome sequencing (WES) may miss certain variants residing outside the coding regions [19]. Pieces of evidence suggest oncogenesis typically involves interplay between germline and somatic variants and different modes of action of non-coding variants could further potentiate these developments. Thus, a systematic approach to unraveling the roles of the non-coding genome in cancer progression should help improve cancer diagnosis and therapy [20].

2. Cancer Genomics and the Emergence of Precision Oncology

As a matter of fact, changes in vulnerable genes involved in cell growth, proliferation, death, or differentiation appear to be essential for all the changes in cell behaviors and remain the most fundamental feature of all cancers, so cancer has to be seen as a genetic disease to be treated accordingly for better outcomes. Over the years, technological advances in the field of molecular biology have been exploited to unravel genomic changes to fully understand the pathogenesis of human cancer. The range of cancer-causing mutations is known to be huge, and 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. Moreover, it has long been observed that every patient responds differently to particular treatments despite having the same type and stage of cancer. These observations have been compelling and led researchers to adopt a precision medicine approach to cancer therapy necessitating the study of genetic features of vulnerable individuals for a patient-specific treatment regimen towards the most effective treatment of cancer [21]. 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. 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 field of cancer research that takes into account the genetic specificities of the individuals for a possible cure. [22]. The term, precision oncology has been coined for the specific clinical oncology practice that relies upon genomic profiling of individual tumors for a complete molecular characterization of the transformed cells and tissues to identify and target specific molecular alterations for efficient cancer therapy [23]. Thus, precision oncology intends to bring a perfectly planned cancer therapy by designing a custom-tailored treatment regimen for vulnerable individuals by identifying their unique needs for the best possible results. The effectiveness of precision oncology has been tested through progressive clinical trials on different tumor types and recent precision oncology trials that include the NCI-MATCH (Molecular Analysis for Therapy Choice) or the NCI-MPACT (Molecular Profiling-based Assignment of Cancer Therapy) have helped shift the focus from cancer treatment based on type and origin to targeting cancer-specific genetic mutations for cure [24]. The discovery of imatinib for the treatment of chronic myeloid leukemia virtually marks the beginning of precision oncology management. Thus, the good use of precision

oncology in clinics began about 25 years ago, but has significantly improved the effectiveness of cancer treatment and is about to enter the mainstream of clinical practice. [25].

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, prognosis, and treatment which have proven to be immensely helpful in advancing precision oncology [26]. There are many potential biomarkers in cancer. and many prognostic biomarkers are therapeutic targets for cancer treatment.

3. Molecular Basis of Cellular Reprogramming and Cancer Therapy

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 cancer cells, and no gene change is thought to be common to all cancers [27]. 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, observations 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 involve 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 in promoting 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 andis often involved in promoting invasion and metastasis Cancer cells can develop novel mechanisms for evading apoptosis and autophagy and new discoveries direct toward the possibleinterrelationship 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. Furthermore, cancer cells maintaining constant proliferative capacity may be guided by their transformation into everlasting non-senescent cells. In this regard, telomeres are the specific repeating DNA structures found at the ends of the chromosome of the cell, which protect the genome against unnecessary nucleolytic degradation, recombination, repair, and interchromosomal interactions. Telomeres are maintained by telomerase which adds nucleotides to telomeres to keep them from getting shorter. Germ cells typically express high levels of telomerase to maintain telomere length. In somatic cells, telomere length usually decreases with the lapse of time, leading cells to undergo senescence with age. Loss of cells in this way generally acts as a barrier to tumor growth which the transformed cells escape as they maintaintheir telomeres despite repeated cell divisions because these cells are able to express a lot of active telomerase. Telomerase has become a potential target in cancer therapeutics as they are over-expressed in transformed cancer cells and cancer stem cells in diverse forms of malignancies. Telomere maintenance mechanisms (TMM) are used by cancer cells through telomerase activation and sometimes by alternate means called alternative lengthening of telomeres (ALT).to avoid apoptosis. Anti-telomerase therapeutics have been developed to selectively target cancer cells to induce cell death by apoptosis without affecting normal cells [28].

An important feature of cancer is that the population of cells that make up cancer is profoundly heterogeneous at the genetic, and epigenetic levels. Tumors usually represent a heterogeneous mass of distinctly differentiated cells that include 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 that generally involve genetic alterations. Tumors develop this feature mainly because the cancer genome is unstable due to accumulating numbers of cancer-causing gene mutations. Genomic instability further promotes genetic diversity by providing the raw material for the generation of tumor heterogeneity [29]. There are transposable elements (TEs) present in the cells called 'jumping genes', the repetitive sequences of DNA that move from place to place in the genome by different means. and represent almost half of the human genome. They represent a powerful means of genetic modification and have played an important role in the evolution of genomes. TEs are typically regulated since the early stage of development and throughout the lifespan by epigenetic mechanisms such as DNA methylation and histone modifications and are crucial for maintaining genomic stability through the regulation of transcriptomic and proteomic profiles of the cell. Dysregulation of TEs has been implicated in different types of human cancers, with the possibility of chromosomal aberrations, oncogenic activation, transcriptional dysregulation, and non-coding RNA aberrations as potential mechanisms underlying the development of cancer. Further, there are fragile points in every genome where the DNA is more likely to be mutated when the genome is replicated. These breakage points have frequently been linked to genetic and heritable disorders like cancer. Moreover, there can be mutations present in certain genes, known as mutator mutations, that further increase the inherent rate of genomic changes, resulting in even greater genetic instability that leads to the accumulation of multiple oncogenic mutations within a cellular lineage. Not all such changes are "malignant", but the rate of such development could translate into cancer manifestation at different stages in a lifetime. Mutator mutations and genetic instability are generalized concepts in cancer genetics, referred to as mutator hypothesis, that relates to those few mutations that lead to an enhanced rate of the gene mutations leading to chromosomal instability, microsatellite instability, and deregulation of 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 relevant measures for prevention and cure. 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. Researchers have begun examining the genomic data of vulnerable individualsto allow clinicians to embark on the path of personalized radiation therapy.

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 bythe 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 [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].

4. Targeting Genetic Alterations in Medical Oncology

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 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. 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 the 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 findings have revealed many crucial genes and proteins associated with the pathways of cancer reprogramming which could be taken as attractive targets for precise cancer treatments. These molecules are thought to participate in crucial cellular events in different ways eventually leading to uncontrolled cell growth and proliferation responsible for tumor growth in our bodies. A few common alterations that are frequently implicated in cancer progression with profound effects are detailed below.

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 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 to 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 of maintaining 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 [43].

A series of growth factors and their receptors are involved in cancer development and metastasis. Receptor tyrosine kinases (RTKs) are a class of receptors for many polypeptide growth factors, cytokines, and hormones that can play vital roles in cancer development. RTKs are cell surface receptors with specialized structural and biological features capable of dimerizing with other adjacent RTKs leading to rapidly phosphorylating tyrosine residues on target molecules to initiate several downstream biochemical cascades in the affected cells. RTKs like Fibroblast growth factor receptor (FGFR), Epidermal growth factor receptor (EGFR), Platelet-derived growth factor receptor (PDGFR), and Vascular endothelial growth factor receptor (VEGFR) control vital functions such as cell growth, proliferation, differentiation, apoptosis, inflammation, and stress responses. These cellular processes can be critical for reciprocal interactions between tumors and stromal cells and play a central role in the control of

tumor formation, angiogenesis, and metastasis [44]. The multifaceted role of RTKs makes them suitable candidates for selective targeting in cancer therapy but their involvement with alternate pathway activation often presents serious challenges to anti-RTK therapy.

The trimeric GTP-binding protein (G protein) mediated signaling is critical to many cellular processes and minor defects in the related pathways 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, which remain attached to the cytoplasmic face of the plasma membrane, 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 specifically associate 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 [45]. 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). 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 number 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 [47]. 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.

The nuclear factor erythroid 2 (NFE2)-related factor 2 (Nrf2) belongs to CNC (cap‘n’collar) family proteins, a group of basic leucine zipper (bZip) transcription factors encoded by basic leucine zipper (bZIP) genes, which serves as the master regulator of the cellular antioxidant response. Recent studies have revealed many new roles for Nrf2 in the regulation of essential cellular processes through 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 chemopreventive 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 [48].

The insulin-like growth factor receptor (IGF-1R), is an RTK that binds IGF1 with a high affinity and is an important factor in the growth, differentiation, and survival of cells in health and disease. IGF-1R plays an important role in the anchorage-independent growth of cells, which may enable cancer cells to survive and grow in the absence of anchorage to the extracellular matrix (ECM) and the neighboring cells. High gene expression level for IGF-1 and IGF-1R have been associated with the upregulation of pathways supporting cell growth and survival, cell cycle progression, angiogenesis, and metastatic activities during cancer development, and is considered essential in many cancer types [49].

B-cell lymphoma-2 (Bcl-2) oncoprotein is primarily a cell death regulatory protein that controls whether a cell lives or dies by apoptosis. 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 crucial roles in oncogenesis. An aberrant expression of the BCL2 gene may keep cancer cells from dying and is frequently implicated in prolonged cell survival and therapy resistance in human cancer. The Bcl-2 family proteins form subgroups, one of which may inhibit cell death and prolong cell survival by 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 upregulation of pro-survival Bcl-2 proteins. The important role played by Bcl-2 family proteins in cancer development renders them potential targets for the 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 BH3-mimetic drugs may prove to be novel agents for cancer therapy.

5. Signaling Pathway Deregulation and Prospective Targets for Cancer Therapeutics

The root cause underlying cancer progression is genetic and 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 signaling network as the foremost system of communication between cells and the surroundings that

involve a variety of chemical and mechanical signals to regulate different signaling pathways comes into consideration here as all the essentials of cellular behaviors like cell growth and proliferation, cell polarity, cell metabolism, differentiation, survival, and migration can be seen guided by the components of these pathways working in a collaborative manner in the cell. The signaling pathways together maintain an internal circuitry inside cells guided by external stimuli enabling them to 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]. Almost all gene modifications can be related to one or more of these signaling pathways that are deregulated in the affected cells to acquire hallmark properties of cancer. Cancer cell signaling displays altered expressions of the components of the signaling network that include many secreted protein receptors, growth factors, protein kinases, phosphatases, different cytoplasmic proteins, and transcription factors leading individual cells to respond to the changes with appropriate physiological behaviors. Cell division is mainly regulated by a group of extracellular growth factors that signal resting cells to divide by exploiting the intrinsic regulatory process of the cell. 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 camefrom 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. Theoncogenic 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. Many of these mutations have been directly linked to the growth factors and their receptor proteins involved with tumor growth, angiogenesis, invasion, and metastases [55,56].

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 EGFR, FGFR, IGFR, VEGFR, 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 process evidently presents the option for crosstalk between components of different signaling pathways at different stages of the cellular process. A molecule participating in crosstalk can affect the activation of alternate signaling pathways, and receptors can also have an altered ability to bind to the ligands which can 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 the estrogen receptor (ER), EGFR/HER, or IGFR, but in many cases, molecules and intermediates of multiple signaling pathways can be interactively involved in the process. In this way, the many signaling molecules affecting cancer cells together could beconsidered to create elaborate

integrated circuits within the cell, derived from the usual signaling circuits that operate in normal cells. The transformed intracellular circuit could be divided into distinct subcircuits specialized in specific cellular activities to promote hallmark features of cancer [57] (Fig. 1). Signal transduction leading to tumor growth, cancer cell migration, metastasis, and drug resistance are often complex processes, as cancer cells typically develop abnormalities in multiple signaling pathways or rely on crosstalk between different pathways and some redundant pathways for maintenance of growth and survival.

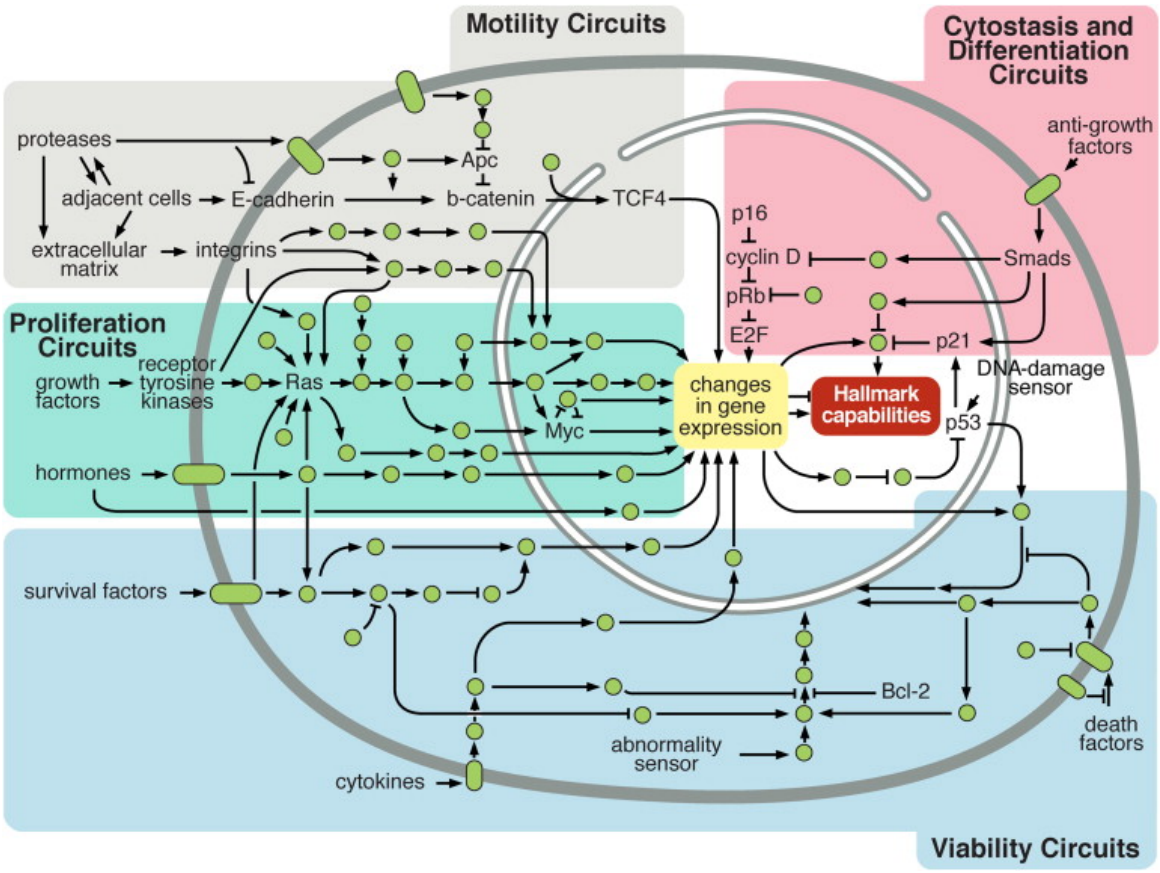

Figure 1. Intracellular Signaling Networks Regulate the Operations of the Cancer Cell.
An elaborate integrated circuit operates within normal cells and is reprogrammed to regulate hallmark capabilities within cancer cells. Separate sub-circuits, depicted here in differently colored fields, are specialized to orchestrate the various capabilities. At one level, this depiction is simplistic, as there is considerable crosstalk between such sub-circuits. 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]. With permission from Elsevier)

As cancer progression involves alterations in signaling pathways due to mutations in the relevant genes, it is satisfying and mechanistically well-founded that a therapeutic intervention taking into account this biology of the affected cells can pave the way for a very effective cancer treatment [58,59]. Further, it has been established in clinical practice that targeting a single intermediateor pathway brings considerable results toward recovery, possibly because it impedes the synergistic signaling process of disease progression. Yet, the constitutive activation of a molecular event that contributes to cancer development can be sustained by different

mechanisms, and strategies to inhibit multiple targets or redundant pathways simultaneously with molecular-targeted agents could prove to be an even more effective way to treat cancer and overcome resistance in cancer therapy [60]. It has indeed been tried with anticipated outcomes in some forms of cancer, indicating the need for more research in that direction. The representative signaling pathways involved in cancer cell reprogramming and the scope for therapeutic targeting of the signaling molecules and intermediates for efficient cancer treatment 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 proteins. It may act as a molecular switch that controls 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 the evolutionarily conserved signaling system that is activated by MEK. It is activated by Raf which, in turn, is targeted 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 are ongoing for the efficacious treatment of the disease [63].

PI3K/Akt/mTOR signaling pathway: This pathway can be 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 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 by participating in multiple signaling pathways inside the cell and is actively involved in cell growth, proliferation, autophagy, and apoptosis. The canonical pathway of mTOR activation depends on signaling through PI3K/Akt, though alternative non-Akt dependent activation through the MAPK pathway is now so well recognized. 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 a variety cell behaviors. Persistent mutational activation of the PI3K/Akt/mTOR

pathway in the absence of different stimuli has been frequently observed in many cancers. Several mTOR inhibitors have also been developed to treat cancer, and some are being evaluated in clinical trials for approval [64,65]. In addition, Phosphatase and tensin homolog (PTEN)), a potent tumor suppressor, is a crucial component of this pathway that can work independently as a phosphatase against phospholipids and proteins. Its primary target is PIP3, the direct product of PI3K which is crucially involved in the signaling process. Mutational deregulations of the PTEN/ PI3K network have been associated with many cancer types including familial cancers. It is a potential means of targeting PI3 K-mediated signaling in cancer therapeutics [66]. Adaptive resistance to the pathway inhibitors is common, and combination therapy, if well tolerated, may produce favorable anticancer results [67].

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 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 [68,69]. 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 [70]. 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 [71,72].

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 malignancies. Furthermore, the classical, SMAD-independent pathway of TGF-β receptors may engage in crosstalks with other signaling pathways, such as Wnt/β-catenin, Ras/RAF/MAPK, and PI3K/Akt/mTOR pathways, to play vital roles in carcinogenesis, and a proper understanding of the TGF- β signaling pathway in cancer progression would resolve controversies related to the signaling pathways [73,74]. 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 [75,76].

The Hippo Signaling Pathway: Hippo Pathway is an evolutionarily conserved major signaling pathway originally identified in fruit flies (Drosophila melanogaster) and controls contact inhibition and organ size development. It is a serine/threonine kinase signaling cascade and its dysregulation 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 malignant growth. The canonical Hippo pathway comprises 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 translocates 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 [77]. 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 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 [78.79].

Wnt/β-catenin Signaling Pathway: This signaling pathway 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-protein binding to the extracellular domain of a Frizzled (Fz) family receptor, a distinct family of GPCRs that generally do not involve activation of G proteins, to relay signals through the cell via different paths to influence a variety of cellular mechanisms critical to cancer development. The Wnt pathway has been formally divided into theβ-catenin dependent canonical pathway and the β-catenin independent, non-canonical Planar cellpolarity (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 activationof β- catenin preventing excessive cell growth and tumor formation. The APC/β-catenin pathwayis 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, indicating an overlap with several tumor-promoting pathways. Mutations that prevent the degradation of β-catenin, including certain mutations in β-catenin or the APC component of the β-catenin destruction complex and others distort the regenerative pathway to contribute to cancer progression and metastasis [80]. Deregulation of the signaling pathway results in alterations in cell growth and survival, maintenance of cancer stem cells, metastasis, and immunecontrol which have been linked to both solid and hematological tumors. The activation of the non-canonical pathway generally involves the recruitment of Rho family small GTPase that leadsto enzymatic rearrangements of the cytoskeleton and/or certain transcriptional activation of effector proteins. Both of these pathways essentially require the binding of Wnt proteins to the Frizzled receptors for the execution of the function.

The Wnt/Ca2+ signaling is followed by G-protein-activated phospholipase C activity leading to intracellular 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. Mutations of the APC gene are observed in about 80% of colon cancers where cancer stem cells (CSCs) are thought to play a critical role in metastasis and relapse, indicating the role of this signaling in maintaining CSC. The role of Wnt signaling in cancer immune evasion and drug resistance is well recognized, and identifying tumor-specific signaling intermediates as targets for drug action can be crucial to effective cancer therapy. Many different agents effectively targeting molecules of this signaling pathway are being explored for the efficacious treatment of different cancer types [81,82].

Hedgehog (Hh) Signaling Pathway: Hh is an evolutionarily conserved signaling pathway and one of a few signaling pathways frequently involved in intercellular communication. It is a key regulator of embryonic development that controls cell patterning, proliferation, and differentiation for organs developments in mammals as well as in the regeneration and maintenance of tissue homeostasis This pathway has frequently been associated with birth defects, stem cell renewal, and cancer. Hh signaling depends on three transmembrane receptor

proteins. Namely Patched, iHog, and Smoothened. Hh proteins are coded by at least three genes in vertebrates that include Sonic, Desert, and Indian hedgehog. 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. There are three different forms of the transcription factor, Gli1. Gli2 and Gli3 are present in vertebrates which may undergo proteasomal processing similar to that of the Wnt pathway to exert their effects in response to appropriate signals. The activated form of Gli moves to the nucleus to bind to their promoters leading to the transcription of the target genes. Mutational changes that lead to excessive activation of the Hh pathway have been implicated in different malignancies. Communication between Hh and major signaling pathways, such as Wnt, Notch, and TGF-β, play crucial roles in the pathophysiology of the disease. Several Hh signaling pathway inhibitors have been developed for a range of cancers, and a few agents are thought to be highly effective for patients with recurrent and advanced cancers [83].

Notch signaling pathways: It is a contact-dependent signaling pathway that has a major role in controlling cell fate decisions and regulating pattern formation during the renewal and development of most tissues and performs major tasks during the embryonic development of animals. Signaling is mediated through the Notch receptor protein, a single-pass transmembrane protein that undergoes successive proteolytic cleavage steps upon activation to perform its action. Notch is activated in a contact-dependent manner by the specific signal protein called Delta, present on the neighboring cell that leads to the cleavage and release of its cytoplasmic tail, notch intracellular domain (NCID) which translocates to the nucleus where it regulates expression of the target genes [84]. Notch signaling is associated with the regulation of many cellular processes like cell proliferation, survival, differentiation, and apoptosis through cell-to-cell communication crucial to the development of many tissues. The signaling pathway is a key regulator of self-renewal and differentiation of many cell types and is known to be an important regulator of Hematopoiesis. Notch acts as a context-dependent binary cell-fate-determining pathway and its hyperactivation has been implicated in the oncogenic stimulation of many solid and hematological cancers.

The Hh and Notch signaling pathways are the active regulators of communication between cells and are actively involved in EMT regulation that is critical to organ development, regeneration, stem cell maintenance, and tissue homeostasis. The self-renewal potential of cancer stem cells (CSCs) has been attributed to these signaling pathways crucial to maintaining CSCs in the tumor mass that causes disease progression, recurrence, and chemoresistance. Importantly, the Hippo pathway has been found to repress Wnt signaling stimulation which could induce cancer stems cell activities. In addition to that, 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 [85]. 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 presents the option to identify the signaling intermediates with confirmed hyperactivities as potential targets in anti-CSC drug discovery for effective cancer treatment. Selective targeting of these pathways along with other proliferative pathways such as the PI3K/Akt or RAS/RAF/MAPK pathways could prove to be an effective strategy for combination therapy of cancer [86, 87].

The NF-κB signaling pathway: This pathway 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 [88]. Constitutively activated NF-κB signaling may lead to inflammation-related disorders, and its role in pathological inflammation and cancer development is well recognized now [89]. 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 [90]. 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 [91,92]. 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 [93,94].

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 [95,96]. 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 [95]. cGAS–STING signaling may also induce autophagy and additionally communicate via p53, MAPK p38, and STAT3 signaling in a context-dependent manner [9]. 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 [97].

Rho/ ROCK signaling pathway: The components of the Rho/ Rho-kinase (ROCK) signaling pathway are established as the potential regulators of the cell's actin cytoskeleton and dynamics.

ROCKs (ROCK1 and ROCK2) belong to the AGC (PKA/ PKG/PKC) family of serine-threonine specific protein kinases which is a downstream effector of the small guanosine triphosphatase (GTPases), RhoA, B, and C, and actively participates in a variety of cellular activities controlled by the actin cytoskeleton including cell polarity, cell contraction, cell cycle progression, proliferation, motility, and invasion. Aberrant Rho/ROCK signaling has been convincingly implicated in several cancer types owing to its ability to enhance tumor growth, cell migration, metastasis, and extracellular matrix remodeling [98]. Molecular inhibitors are being developed to target ROCK1, ROCK2, or both, with high clinical value for the treatment of advanced solid cancers. Moreover, the different activities of ROCK in the immune system make it a potential target in cancer immunotherapy, so ROCK is thought to be of great value in cancer therapeutics. A deeper understanding of this pathway may add new dimensions to future precision cancer therapy [99]

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

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 [100]. 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 [101]. It forms the basis of precision medicine in general and is at the core of the development of precision oncology. The breakthroughs in high-throughput technologies in recent years have led to the rapid accumulation of large-scale omics cancer data and brought an evolving concept of “big data” in cancer the analysis of which requires huge computational resources with the potential to bring new insights into critical problems. The combination of big data, bioinformatics, and artificial intelligence is thought to lead to notable advances in translational research in cancer [102,103].

Artificial intelligence: Artificial intelligence (AI) encompasses multiple technologies with the common aim of computationally simulating human intelligence to solve complex problems. It is based on the principle that human intelligence can be defined in a way that a machine can easily mimic and execute tasks from the simpler to far more complex ones successfully [104]. Broadly referred to as computer programming enabled to perform specific tasks, the term may be applied to any machine that displays traits associated with human understanding, such as learning and problem-solving. In regular programming, data are processed with well-defined rules to bring solutions, whereas AI relies on the learning process to devise rules for the efficient processing of data to yield smart results. AI and related technologies have increasingly been prevalent in finance, security, and society, and are now being applied to healthcare as well [105]. It has been widely applied in precision medicine-based healthcare practices and is found to be greatly useful in medical oncology practice. 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 knowing 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 advances in NGS have 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, integrating multi-omics-related studies with artificial intelligence is the need of the hour and is likely to serve the purpose well with time. 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 for anticipated results. Thus, the advances in AI 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 are mostlikely to help many more problems in this direction to be resolved swiftly. In this way, AI is thought to be the future of precision oncology towards the prevention, detection, risk assessment,and treatment of cancer [106,107].

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 [108]. Therefore, the most common and purposeful application of traditional machine learning in healthcare seems to be in the area of precision medicine and is most suited for the data-driven identification of cancer states and designing treatment options that is crucial to precision oncology-based cancer treatment [109].

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, multi-omics-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 processing several pieces of information received from many different sources to translate into a particular reflex action. In DL, the same concept of a network of neurons is imitated on a machine learning platform to emulate human understanding to bring perfect solutions. The neurons are created artificially in a computer system and the data processing layers work together to create an artificial neural network where the working of an artificial neuron could be taken as like that of a neuron present in the brain. Thus, DL is designed to use a complex set of algorithms enabling it to process unstructured data such as documents, images, and text to find efficient results [110].

The effective development of drugs for the treatment of cancer is a major problem in cancer research and DL provides immense help to researchers in this regard. 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 the 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. Occupation-oriented pharmacology is the dominant paradigm of drug discovery for the treatment of cancer. It relies on the use of inhibitors that occupy the functional binding site of a protein and can disrupt protein interactions and their functions. 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 [111]. 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. 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 almost every known organism on the planet [112,113]. 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. A newly developed DL system called PocketMiner is an efficient tool for predicting the locations of bonding sites on proteins. Proteins exist in a state of dynamic equilibrium with their different conformational structures, including experimentally determined structures that may not have targetable pockets. PocketMiner uses graph neural networks to find hidden areas or pocket formation from a single protein and is thought to be 1,000 times faster than existing methods of finding binding sites on proteins. This technology has made researchers understand that around half of proteins that were earlier considered undruggable might have 'cryptic pockets' that could be targeted successfully by anticancer agents. The AI-based system finds multiple uses in cancer management like the prediction of treatment response, estimation of survival analysis, risk estimation, and treatment planning, and is becoming the central approach in precision oncology [114].

7. The Cancer Genome Atlas (TCGA) Program and Related Cancer Initiatives

The National Institutes of Health (NIH) has taken the lead role in cancer research and is the largest funder of cancer research in the world. The National Cancer Institute (NCI), the leading cancer research enterprise is part of NIH and is committed to exploiting basic cancer research into efficacious cancer therapies. In this regard, the Cancer Genome Atlas (TCGA) Program is the landmark cancer genomics program initiated by the NIH, and 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 is a joint effort by the NCI and the National Human Genome Research Institute (NHGRI), also a part of NIH, that began working in 2006 and has 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 [115,116]. Considering the genes and pathways affecting different cancer types and individual tumors vary considerably, a complete understanding of these alterations becomes essential to identify vulnerabilities and discover precise therapeutic solutions. A comprehensive analysis of tumors based on their genomic studies must reveal the alterations in signaling pathways indicating patterns of vulnerabilities and the means to identify prospective targets for the development of personalized treatments and new combination therapies. The TCGA ResearchNetwork has profiled and analyzed a large number of human tumors to discover molecular aberrations at the DNA, RNA, protein, and epigenetic levels and thereby provided reliable diagnostic and prognostic biomarkers for different cancer types since then.

As our understanding of biochemical signaling has grown and the range of possible

treatment options expands, it is essentially required to have biomarkers to accurately predict how patients will respond to specific treatment regimens, which is a vital need for precision oncology. Circulating DNA and extracellular vesicles are abundantly released by cancer cells that can be obtained by liquid biopsies and are excellent sources of a variety of molecular markers. Molecular profiling of these markers can be used to gain crucial information regarding cancer development including tumor heterogeneity. Genomic analysis of tumors has certainly become the mainstay in cancer care, and applying it to oncological practice needed a clinical support system that could swiftly predict the clinical implications associated with specific mutations. It led to the development of OncoKB, an expert-guided precision oncology knowledge base developed at Memorial Sloan Kettering Cancer Center (MSKCC), in New York which is among the first to have been recognized as the NCI-Designated Cancer Centers as part of the national cancer program of the federal govt. that started in 1971. OncoKB's curated list of cancer genes with detailed comments is available on its public web resource (http://oncokb.org, which has been incorporated into the cBioPortal for Cancer Genomics (https://www.cbioportal.org/) to provide visualization, analysis, and download of large-scale cancer genomics data sets allowing researchers to gain a thorough understanding of the genomic alterations involved in cancer development. The public cBioPortal site is hosted by the Center for Molecular Oncology at MSKCC and maintained by a multi-institutional team consisting of MSK and others. 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 precise techniques to fulfill the purpose involved with the big-data studies satisfactorily [117,118].

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 help gain insights into 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 [119,120]. It is based on the consideration that possible observable combinations of those mutations must converge to a few hallmark signaling pathways and associated networks responsible for cancer development. In this way, the proposed framework aims to analyze the available 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 progression and direct treatment planning accordingly. In this regard, 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 [121,122]. Analyzing over 11,000 tumors from the most prevalent forms of cancer, and focusing on how germline and somatic variants collaborate in cancer progression, the Pan-Cancer Atlas has so far provided a most comprehensive and in-depth understanding of how and why tumors arise in humans [123,124].

The synchronizing view of 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 also present novel biological and clinical insight for cancer stem cell-targeted therapies [125,126]. 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 receive precisely designed treatment for cancer. 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.

Besides that, the Cancer Cell Mapping Initiative (CCMI), originally founded in 2015 by researchers from the University of California, San Francisco, and the University of California, San Diego, has been dedicated to generating complete maps of major protein-based genetic interactions underlying cancer progression and attempts to develop computational methods using these maps to identify novel drug targets and patient groups with common outcomes. It 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 [127]. 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 [128]. Furthermore, the Broad Institute of MIT and Harvard's Cancer Dependency Map (DepMap)initiative, an academic-industrial partnership program formally announced in 2019, is devoting its research to accelerate precision cancer medicine by creating a comprehensive map of tumor vulnerabilities and identifying key biomarkers of cancer. DeepMap initiative is focused on screening thousands of cancer cell lines by the use of RNA interference (RNAi) and CRISPR- Cas9 loss-of-function gene-editing strategies to identify genes whose expression may have been found to be essential for cancer cell development. CRISPR-Cas9 gene editing is an efficient method for genome modification for nearly all cell types. CRISPR editing and screening have emerged as powerful tools for investigating almost all aspects of cellular behaviors and have greatly impacted our understanding of cancer biology and continue to contribute to new discoveries.

A related project called, Cancer Cell Line Encyclopedia (CCLE) project was initiated as a collaboration between the Broad Institute, and the Novartis Institutes for Biomedical Research in 2008 aimed at large-scale genetic characterization of thousands of cancer cell lines to link characteristic genetic alterations with distinct pharmacologic vulnerabilities, and to translate cell line integrative genomics into cancer patient stratification. By access to critical genomic data such as gene mutation, copy number variation, gene expression, and methylation profiles from the CCLE, scientists can now predict novel synthetic lethality and identify new molecular markers whose selective targeting can control cells that possess specific genetic mutations. In this way, the initiative has provided a rigorous foundation on which to study genetic variants, and candidate targets, design anticancer agents and identify new markers-driven cancer diagnoses and therapies [129]. By all such means, the field of cancer genomics can be seen as constantly evolving to help cancer-causing changes be identified to gain a better understanding of the molecular basis of cancer growth, metastasis, and drug resistance, and translate cancer

research into new cancer therapeutics.

8. Single-cell Technology to Unmask Tumor Heterogeneity

The tumor is an abnormal mass of tissue that appears due to unregulated growth and division ofcells which successfully avoid senescence. A tumor is benign till it is limited to its original position and becomes malignant or cancerous when capable of growing and spreading to other parts ofthe body. Tumor heterogeneity is a hallmark property of cancer development and broadly refersto the differences between tumors of the same type in different patients, the differences betweena primary and a secondary tumor, and the differences in genomic and phenotypic profiles displayed by cells within a single tumor. 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]. Tumor heterogeneity appears to be a critical phenomenon in the history of individual cancers, as its translational significance may reflect on tumor progression, disease recurrence, treatment response, and resistance [132]. Recent investigations on drug resistance and tumor heterogeneity have confirmed 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 advanced treatment strategies for cancer [133,134]. More precisely the cellular composition of a tumor is known, the underlying mechanism of disease progression is understood, and/or molecules and pathways involved in the process are identified, and more specific therapeutic strategies could be devised to get the desiredresult. It is the stated goal of precision oncology 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 mutational profile of the affected cells to better understand the molecular consequences of different variants presentin the tumor. 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 identifying somatic SVs, understanding genomic rearrangements and unmask tissue heterogeneity. Moreover, single-cell sequencing can also be combined with CRISPR knockout screening 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 to fully understand the underlying cellular events [137]. Combining the CRISPR-Cas system with single-cell techniques for studying gene functions with the concurrent use of single-cell resolution techniques, such as flow cytometry, microfluidics, manual cell picking, or micromanipulation, can be exploited in cancer research in many ways, including identifying novel drug targets, studying unknown mechanisms of action of drugs and designing treatment regimen [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 tumor suppressor genes. Abnormal epigenetic changes are usually influenced by aging, viruses, and dietary and environmental factors that frequently contribute to cancer development. 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 single-cell epigenome profiling holds great possibilities for deciphering the cellular states and characterizing tumor heterogeneity with an option for therapeutic interventions to pin specific mutations having profound effects on epigenetic pathways. 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.

Single-cell sequencing technologies have largely been successful in leading scientists to understand the cell types and features associated with the tumor yet, the spatial context of this development is essential to better understand how cells organize and communicate across the tissue to fully unlock the repertoire of tumor heterogeneity. It requires 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. This is an essential part of spatial biology and adds another dimension to single-cell analysis to unmask tumor heterogeneity [140,141]. Spatial biology simply tries 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 multi-omics technologies allowing researchers to measure all the gene activity in a tissue sample and assay the genetic information of single cells within their native tissue environment [142,143]. The growing ability to demonstrate the role and function of distinct cell types present in the tissue has paved the way for a new understanding of the tissue-specific cellular pathways and interactions that lead to cancer manifestation.

Thus, molecular analysis of cancer cells based on single-cell technologies aims to present an accurate picture of the most recent developments regarding changes in genes and proteins responsible for alterations in cellular processes, enabling a better understanding of prognosis and pathways of development of cancer. New advances in multi-omics techniques powered by AI h now enable researchers to integrate genomic, transcriptomic, epigenomic, and other related data to gain the most accurate information on the activity state of individual genes and proteins to reveal the 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 likely to streamline future research directions.

9. Precision Oncology and Targeted Drug Therapy of Cancer

Targeted drug therapy is the form of cancer therapeutics that targets specific genes and proteins of cancer cell reprogramming, the signaling molecules, and others in the tumor microenvironment that contribute to cancer development. This contrast with the single-target approach employed in chemotherapy to primarily target and kill actively dividing cancer cells with serious side effects and so the emergence of targeted drug therapy can be seen as a natural outcome of decades of studies on molecular reprogramming of affected cells in different cancers. Some noticeable breakthroughs have come in certain cancers as a renewed understanding of the signaling pathways underlying cancer development has led to the development of specific targeted drugs that have really revolutionized the treatment of cancer. This form of cancer therapy can be thoroughly optimized by means of precision oncology that enables taking advantage of genomic profiling of patient samples for insights into the mutational changes underlying pathway alterations responsible for cancer initiation and progression [146]. Precision oncology-based treatment strategies pledge to diagnose and prognosis the disease using specific molecular-level information about a patient's tumor to treat the ill with desired results. Inthis way, it qualifies to be a theranostic approach to cancer treatment satisfactorily. The term, theranostics literally means a combination of diagnosis and therapeutics and refers to the pairing of diagnostic methods such as the proteogenomics approach to biomarker discovery, with appropriate therapeutic interventions for effective management of the disease. Theranostics focuses on patient-centered care and thus provides a transition from conventional to personalized medicine for targeted, efficient and safe pharmacotherapy relevantly applicable in precision oncology [147,148].

The anticancer drugs employed in targeted therapy are mainly 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 [149]. They are broadly classified as monoclonal antibodies (mAbs) and small-molecule drugs. The small molecule drugs are designed to directly approach the cell membrane and interact with targets inside the cell and usually inhibit the enzymatic activity of target proteins such as the proteasome complex, cyclin-dependent kinases and a variety of signaling proteins. Kinase family proteins such as tyrosine kinases, Rho kinase, Bruton tyrosine kinase, ABL kinases, NAK kinases, etc. play an essential role in modulating signaling pathways associated with cancer progression and therefore constitute a valuable source of biological targets against cancers (Table 1). A type of targeted therapy, called tumor-agnostic therapy uses drugs and other substances to target cancer-specific genetic changes or markers to treat the problem without requiring focusing on the cancer type or where the disease may have started in the body.

Table 1. List of Protein Kinase Inhibitors approved by FDA.
(NRY, non-receptor protein-tyrosine kinase; RTK, receptor protein-tyrosine kinase; S/T, protein-serine/threonine kinase; T/Y, dual-specificity protein kinase)

Protein kinase inhibitor	Approval year	Primary targets	Target kinase family	Indications
Abemaciclib	2017	CDK4/6	S/T	Breast cancer
Acalabrutinib	2017	BTK	NRY	Lymphoma

Afatinib	2013	ErbB1/2/4	RTK	Lung cancer
Alectinib	2015	ALK, RET	RTK	Lung cancer
Avapritinib	2020	PDGFR	RTK	Gastrointestinal Cancer
Axitinib	2012	VEGFR1/2/3	RTK	Kidney cancer
Binimetinib	2018	MEK1/2	T/Y	Melanoma
Bosutinib	2012	BCR-Abl	NRY	Leukemia
Brigatinib	2017	ALK	RTK	Lung cancer
Cabozantinib	2012	RET, VEGFR2	RTK	Thyroid. kidney, hepatocellular cancer
Capmatinib hydrochloride	2020	c-MET	RTK	Lung cancer
Ceritinib	2014	ALK	RTK	Lung cancer
Cobimetinib	2015	MEK1/2	T/Y	Melanoma
Crizotinib	2011	ALK, ROS1	RTK	Lung cancer
Dabrafenib	2013	B-Raf	S/T	Melanoma; lung, thyroid Cancer
Dacomitinib	2018	EGFR	RTK	Lung cancer
Dasatinib	2006	BCR-Abl	NRY	Leukemia
Encorafenib	2018	B-Raf	S/T	Melanoma, colorectal cancer
Entrectinib	2019	TRKA/B/C, ROS1	RTK	Lung cancer; solidTumors
Erdafitinib	2019	FGFR1/2/3/4	RTK	Urothelial carcinoma
Erlotinib hydrochloride	2004	EGFR	RTK	Lung, Pancreatic cancer
Everolimus	2009	FKBP12/mTOR	S/T	Breast, kidney cancer, Neuroendocrine tumors
Fedratinib	2019	JAK2	NRY	Myelofibrosis
Futibatinib	2022	FGFR2	RTK	Cholangiocarcinomas
Gefitinib	2003	EGFR	RTK	Lung cancer
Gilteritinib	2018	Flt3	RTK	Leukemia
Ibrutinib	2013	BTK	NRY	Lymphoma

Imatinib mesylate	2001	BCR-Abl	NRY	Leukemia; Gastrointestinal
Infigratinib	2021	FGFRs	RTK	Cholangiocarcinoma
Lapatinib ditosylate	2007	ErbB1/2/HER2	RTK	Breast cancer
Larotrectinib	2018	TRKA/B/C	RTK	Solid tumors
Lenvatinib	2015	VEGFR, RET	RTK	Hepatocellular, endometrial, Thyroid, Kidney cancer
Lorlatinib	2018	ALK	RTK	Lung cancer
Midostaurin	2017	Flt3	RTK	Leukemia
Mobocertinib	2021	EGFR with exon 20 insertions	RTK	Lung cancer
Neratinib	2017	ErbB2/HER2	RTK	Breast cancer
Nilotinib	2007	BCR-Abl	NRY	Leukemia
Osimertinib	2015	EGFR T790M	RTK	Lung cancer
Pacritinib	2022	JAK2	RTK	Myelofibrosis
Palbociclib	2015	CDK4/6	S/T	Breast cancer
Pazopanib hydrochloride	2009	VEGFR1/2/3	RTK	Kidney cancer; soft tissue sarcoma
Pemigatinib	2020	FGFR2	RTK	Cholangiocarcinoma
Pexidartinib	2019	CSF1R	RTK	Tenosynovial giant cell tumor
Pirtobrutinib	2023	BTK	NRY	Lymphoma
Ponatinib hydrochloride	2012	BCR-Abl	NRY	Leukemia
Pralsetinib	2020	RET	RTK	Lung cancer
Quizartinib	2023	FLT3/STK1	RTK	Leukemia
Regorafenib	2012	VEGFR1/2/3	RTK	Gastrointestinal, Colorectal, Hepatocellular cancer
Ribociclib	2017	CDK4/6	S/T	Breast cancer
Ripretinib	2020	KIT/PDGFR	RTK	Gastrointestinal cancer
Ruxolitinib phosphate	2011	JAK1/2/3, Tyk	NRY	Myelofibrosis

Selpercatinib	2020	RET	RTK	Lung, thyroid cancer
Selumetinib	2020	MEK1/2	T/Y	Neurofibroma
Sorafenib tosylate	2005	VEGFR1/2/3	RTK	Thyroid, Kidney, Hepatocellular cancer
Sunitinib malate	2006	VEGFR2	RTK	Gastrointestinal, kidney, pancreatic cancer
Temsirolimus	2007	FKBP12/mTOR	S/T	kidney cancer
Tepotinib	2021	Met	RTK	Lung cancer
Tivozanib	2021	VEGFR2	RTK	kidney cancer
Trametinib	2013	MEK1/2	T/Y	Melanoma
Trilaciclib	2021	CDK4/6	S/T	Lung cancer
Tucatinib	2020	ErbB2/HER2	RTK	Breast cancer
Vandetanib	2011	VEGFR2	RTK	Thyroid cancer
Vemurafenib	2011	B-Raf	S/T	Melanoma; histiocytic sarcoma
Zanubrutinib	2019	BTK	NRY	Lymphoma

Therapeutic targeting of DNA damage response (DDR) signaling is another emerging field of targeted cancer therapy that exploits the options of targeting cancer cells with exceeding deficiencies in homologous recombination (HR) signaling which includes 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. These enzymes are essentially involved in the process of single-strand break (SSB) repair whose failure leads to the conversion of SSB into double-strand breaks (DSB) requiring repair by HR to prevent cell death. Such lethal genetic interactions, known as synthetic lethality, can be exploited to develop anticancer therapeutics and the enzymes of DDR signaling fit the needs satisfactorily. Overexpression of these proteins has been witnessed in different cancer types such as pancreatic, prostate, breast, ovarian, and oral cancers, providing scope 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 safely. [150,151].

The therapeutic mAbs are modified monoclonal antibodies that target antigens found on the cancer cells or cytotoxic T-lymphocytes in targeted cancer therapy. mAbs are important in cancer treatment as they may be exploited for potentiating the natural immune system by

successfully mutualizing changes in immunogenicity of the affected cells during oncogenesis. The mAbs may be designed to coat the cancer cells to be opsonized and destroyed by the immune cell, block the activity of different cancer-specific antigens called neoantigens, generated by cancer cells, or inhibit the activities of immune checkpoint proteins that promote immune evasion in cancer development [152,153]. Several immune checkpoint proteins are expressed by immune cells, such as T cells, and cancer cells capable of binding with other partner proteins to help cancer cells escape immune responses. Their activation limits vital immune cell activities like T-cell infiltration and other effector cell functions resulting in tumor formation. CTLA-4 is a checkpoint protein present on the T-cell surface that binds to another protein called B7, preventing T cells from killing other target cells, including cancer cells. Certain mAbs, also called anti-CTLA4 monoclonal antibodies, are used to block CTLA-4 and are widely used as immune checkpoint inhibitors in a variety of human cancers. Different forms of monoclonal antibody-based therapy have proven to be efficacious in cancer treatment and are becoming increasingly important tools in targeted cancer therapy [154,155]. Importantly, cancer cells express a number of protein antigens that can be recognized by cytotoxic T lymphocyte (CTL) T cells, thus providing means for CTL-mediated cancer therapy. Targeting transformed cells by CTL may be crucial to the prevention of both hematological and solid tumors and its roles are being explored in cancer immunotherapy. T-cell transfer therapy, also called adoptive immunotherapy or immune cell therapy is a new form of cancer treatment designed to exploit enhanced anti-tumor immune response of the tumor antigen-specific CTL found in the tumors, and has been tried against neoantigen-possessing cells effectively in recent times. Two types of T-cell transfer therapy, tumor-infiltrating lymphocytes or TIL therapy and CAR T-cell therapy are in use, and both involve harvesting autologous T cells infiltrated into the tumor, growing largenumbers of these cells in vitro, and administering to the patient for desired results. CAR T-cell therapy is similar to TIL therapy except that the T cells are designed to express a type of protein known as CAR (CAR for chimeric antigen receptor) to target specific antigens expressed in cancer cells in the body. Although CAR T cells have significantly improved the landscape for hematological malignancies, it has shown limited results in solid tumors as the solid tumors present certain obvious barriers to adoptive T-cell transfer and localization, but a variety of approaches are being deliberated to overcome these barriers to increase its specificity, efficacy, and safety in the treatment of different malignancies. The development of CAR T cell therapy forsolid tumors has been impaired also because most target antigens are common with normal cells.Research is being directed to develop a ‘toolbox’ of novel chimeric antigen receptors (CARs) that could be programmed to use logic to discriminate between normal and cancerous cells to prevent toxicity. This development could help to overcome some of the barriers to the application of CAR-T cells against solid tumors.

Furthermore, therapeutic cancer vaccines, such as the dendritic cell (DC) vaccine, peptide vaccine, and RNA-based neoantigen vaccines have been developed for inducing CTLs against the antigens in cancer patients and have shown encouraging results. These vaccines can be designed to induce the production of biomolecules capable of targeting the shared antigens expressed by cancer cells through appropriate immune response and, are being investigated for their efficacy as neoantigen-targeted individualized cancer vaccines. Dendritic cells (DCs) are specialized Antigen-presenting cells (APCs) known for their ability to present antigens to T cells, and this property of DCs has been exploited for their application in therapeutic cancer vaccines which have been shown to induce protective anti-tumor activities. [156,157]. Besides that, the transposable elements (REs) usually present in the tumor microenvironment are of potential therapeutic importance to create a pan-cancer vaccine that can aid in the prevention of a range of

cancers. There is an enumerable number of regions with TEs involved with the expression of proteins in the cancer cell. Many of these are shared across tumors of the same type and could provide means for destruction by the immune system. 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 results. Thus, immunotherapy remains the frontline area of cancer research, and precision oncology will be focused on immunotherapy accordingly.

As discussed earlier, a major concern in cancer therapeutics is the proper drug delivery to the affected cells and tissue for the desired 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 (NP)-based systems can be programmed to recognize cancerous cells for selective and accurate drug delivery with increased drug localization, cellular uptake, and bioavailability, avoiding encounters with healthy cells. The newly developed quantum dots (QDs) are the class of heterogeneous fluorescent nanoparticle, nanoscale materials with sizes ranging from 1 to 10 nm, with unique optical properties and optimal surface chemical properties to link with targets such as antibodies, peptides, and other small molecule drugs. Named so as the photoluminescent nanostructures can have fully quantized energy states with superior fluorescence characteristics, they are thought to be more specific and effective methods with wide applications in the diagnostics and molecular targeting of the transformed cells. The NP-based drug delivery system, in general, displays better pharmacokinetic and pharmacodynamic profiles including efficient targeting of cancer cells and reduction in side effects, they are sure to serve the needs of precision oncology-based therapy satisfactorily [158,159]. Further, antibody-drug conjugates (ADC) are a fast-expanding therapeutic strategy designed to selectively deliver drugs to cancer cells. ADCs are monoclonal antibodies linked with small molecule cytotoxic drugs through a chemical linker capable of approaching the cancer cells and attaching 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 featuresof antigen-antibody specificity for efficient drug delivery and are considered to be the magic bullets in targeted cancer therapy [10, 161]. In this way, precision oncology seems to be the best fit for strategizing effective means of targeted drug therapy by exploiting the genomic peculiarities of individuals or a cohort of patients for effective personalized cancer treatment (Fig. 2). Itwill remain dedicated to studying the genetic profile of cancer cells to gain a thorough understanding of the alterations in key signaling pathways and related molecular events during cancer progression, therapy resistance, and recurrence to help improve targeted cancer therapy (Suppl. 1 & 2).

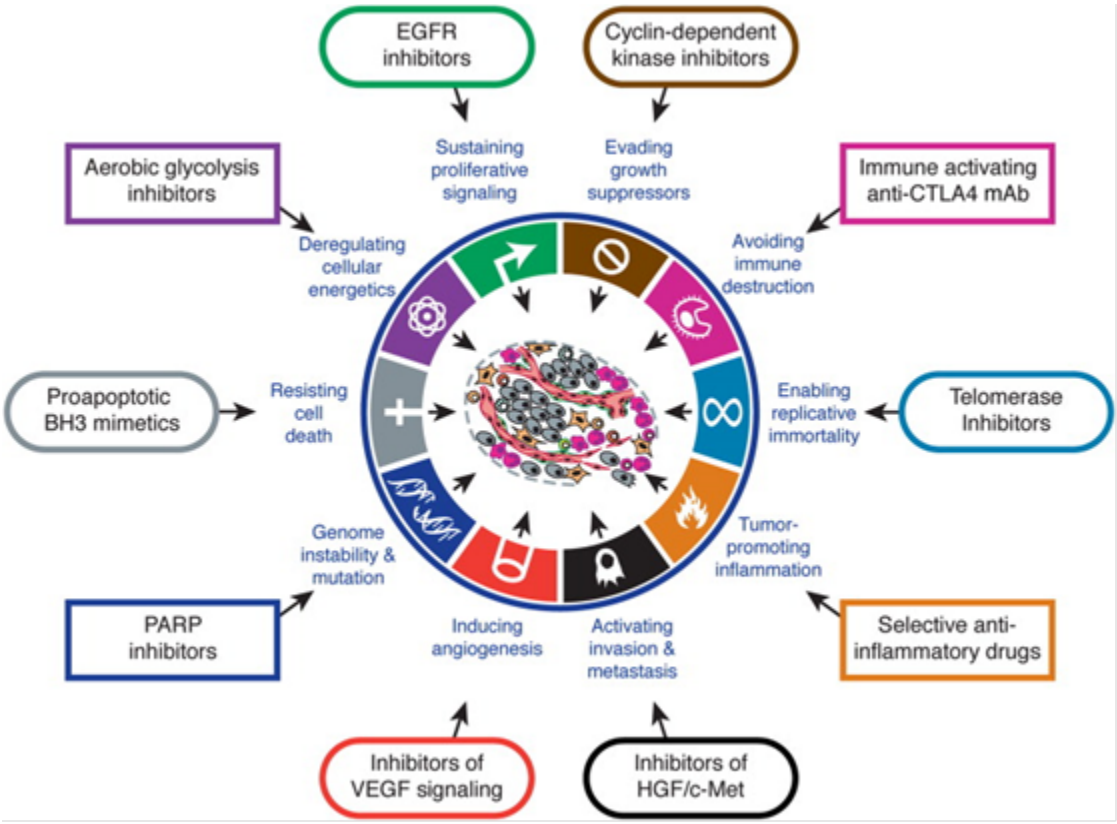

Figure 2. Therapeutic Targeting of the Hallmarks of Cancer
Therapeutic agents that can mitigate the acquired capabilities necessary for tumor growth and cancer progression are being developed for clinical use in treating different cancer types. These drugs are being developed in clinical trials to target each of the emerging neoplastic characteristics and the enabling hallmarks capabilities towards 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]. With permission from Elsevier)

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 willbe needed for future research, drug discovery, and diagnostics to fully unlock its potential and for their application in the management of cancer. Let us not forget that the socioeconomic burden of cancer remains high as the treatment options for most common cancers have been limited so far and is an indication for a renewed approach to expedite 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 extentby 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 [162,163]. Moreover, the move from tissue-based cancer-specific treatments to genome-based targeted treatments entails the reuse of anticancer drugs prescribed for one type of cancer to treat other cancer types as well.It is envisaged that, with the ever-greater understanding of cell signaling mechanisms and geneticalterations in carcinogenesis, considerable progress in cancer treatment will be realized in the near future. Considering that academia, industries, and civil society will be working in

tandem tocater to the contemporary 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 system as a whole [164,165].

10. 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 not very effective in the end. Further, 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. Besides that, 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. Importantly, drug resistance has traditionally been a serious problem in cancer treatment, but the emergence of targeted drug therapy based on precision oncology can greatly improve outcomes. The evolution of gene detection methods, liquid biopsy, and single-cell sequencing technology could facilitate deciphering the molecular mechanism of tumor drug resistance to help develop updated and effective anticancer agents in response to drug resistance. Thus, precision oncology, which relies on the genomic specificity of individuals for successful targeting of the most specific pathways involved in disease progression, is best suited to ensure precise treatment of the disease. This is in fact a natural outcome of cancer genome research, the level of support from multi-omics platforms is most encouraging and it is poised to satisfactorily achieve the intended goal of the cancer initiatives. The growing success of this form of treatment is sure to further strengthen our belief in the possibility of an effective treatment for cancer and it must be made available to an increasing number of people with cancer in order to achieve the goals over time.

Declarations:

Acknowledgements: I acknowledge the consistent departmental support received from the School of Bio Sciences & Technology, Vellore Institute of Technology, Vellore, Tamil Nadu, India, leading to the completion of this work with time.

Authors' contributions: Not applicable

Competing interests: Not applicable

Informed Consent Statement: Not applicable.

Funding: Not applicable

Data Availability Statement: No new data was created, the data analyzed in this study is present in the text and as supplementary materials.

References:

1. Ma X, Yu H. Global burden of cancer. Yale J Biol Med. 2006 Dec;79(3-4):85-94. PMID: 17940618; PMCID: PMC1994799.

2. Clegg LX, Reichman ME, Miller BA, Hankey BF, Singh GK, Lin YD, Goodman MT, Lynch CF, Schwartz SM, Chen VW, Bernstein L, Gomez SL, Graff JJ, Lin CC, Johnson NJ, Edwards BK. Impact of socioeconomic status on cancer incidence and stage at diagnosis: selected findings from the surveillance, epidemiology, and end results: National Longitudinal Mortality Study. Cancer Causes Control. 2009 May;20(4):417-35. doi: 10.1007/s10552-008-9256-0. Epub 2008 Nov 12. PMID: 19002764; PMCID: PMC2711979.

3. Sung, H, Ferlay, J, Siegel, RL, Laversanne, M, Soerjomataram, I, Jemal, A, Bray, F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021: 71: 209- 249. https://doi.org/10.3322/caac.21660

4. Siegel, RL, Miller, KD, Fuchs, HE, Jemal, A. Cancer statistics, 2022. CA Cancer J Clin. 2022. https://doi.org/10.3322/caac.21708

5. Kaluzny AD, O'Brien DM. How vision and leadership shaped the U.S. National Cancer Institute's 50-year journey to advance the evidence base of cancer control and cancer care delivery research. Health Policy Open. 2020 Dec;1:100015. doi: 10.1016/j.hpopen.2020.100015. Epub 2020 Oct 13. PMID: 33073235; PMCID: PMC7550860.

6. Haier, J.; Schaefers, J. Economic Perspective of Cancer Care and Its Consequences for Vulnerable Groups. Cancers 2022, 14, 3158. https://doi.org/10.3390/ cancers14133158

7. Rajpal S, Kumar A, Joe W. Economic burden of cancer in India: Evidence from cross-sectional nationally representative household survey, 2014. PLoS One. 2018 Feb 26;13(2):e0193320. doi: 10.1371/journal.pone.0193320. PMID: 29481563; PMCID: PMC5826535.

8. Cuomo RE, Mackey TK. Policy and governance solutions for ensuring equitable access to cancer medicines in low- and middle-income countries. Ann Transl Med. 2018 Jun;6(11):224. doi: 10.21037/atm.2018.04.26. PMID: 30023387; PMCID: PMC6035971.

9. Cho H, Mariotto AB, Schwartz LM, Luo J, Woloshin S. When do changes in cancer

survival mean progress? The insight from population incidence and mortality. J Natl Cancer Inst Monogr. 2014 Nov;2014(49):187-97. doi: 10.1093/jncimonographs/lgu014. PMID: 25417232; PMCID:PMC4841163.

10. Pilleron, S, Soto-Perez-de-Celis, E, Vignat, J, et al. Estimated global cancer incidence in the oldest adults in 2018 and projections to 2050. Int. J. Cancer. 2021; 148: 601– 608. https://doi.org/10.1002/ijc.33232

11. Rahib L, Wehner MR, Matrisian LM, Nead KT. Estimated Projection of US Cancer Incidence and Death to 2040. JAMA Netw Open. 2021 Apr 1;4(4):e214708. doi: 10.1001/jamanetworkopen.2021.4708. PMID: 33825840; PMCID: PMC8027914.

12. Bayat Mokhtari R, Homayouni TS, Baluch N, Morgatskaya E, Kumar S, Das B, Yeger H. Combination therapy in combating cancer. Oncotarget. 2017 Jun 6;8(23):38022-38043. doi: 10.18632/oncotarget.16723. PMID: 28410237; PMCID: PMC5514969.

13. Kumari S, Sharma S, Advani D, Khosla A, Kumar P, Ambasta RK. Unboxing the molecular modalities of mutagens in cancer. Environ Sci Pollut Res Int. 2022 Sep;29(41):62111-62159. doi: 10.1007/s11356-021-16726-w. Epub 2021 Oct 5. PMID: 34611806; PMCID: PMC8492102.

14. Basu AK. DNA Damage, Mutagenesis and Cancer. Int J Mol Sci. 2018 Mar 23;19(4):970. doi: 10.3390/ijms19040970. PMID: 29570697; PMCID: PMC5979367.

15. Yates, L., Campbell, P. Evolution of the cancer genome. Nat Rev Genet 13, 795–806 (2012). https://doi.org/10.1038/nrg3317

16. Sharma S, Kelly TK, Jones PA. Epigenetics in cancer. Carcinogenesis. 2010 Jan;31(1):27-36. doi: 10.1093/carcin/bgp220. Epub 2009 Sep 13. PMID: 19752007; PMCID: PMC2802667.

17. You JS, Jones PA. Cancer genetics and epigenetics: two sides of the same coin? Cancer Cell. 2012 Jul 10;22(1):9-20. doi: 10.1016/j.ccr.2012.06.008. PMID: 22789535; PMCID: PMC3396881.

18. Geeleher P, Huang RS. Exploring the Link between the Germline and Somatic Genome in Cancer. Cancer Discov. 2017 Apr;7(4):354-355. doi: 10.1158/2159-8290.CD-17-0192. PMID: 28373166; PMCID: PMC5404740.

19. Chang HY. Personal regulome navigation of cancer. Nat Rev Cancer. 2021 Oct;21(10):609-610. doi: 10.1038/s41568-021-00381-x. PMID: 34172966; PMCID: PMC9169632.

20. Zhang X, Meyerson M. Illuminating the noncoding genome in cancer. Nat Cancer. 2020 Sep;1(9):864-872. doi: 10.1038/s43018-020-00114-3. Epub 2020 Sep 14. PMID: 35121955.

21. Doroshow DB, Doroshow JH. Genomics and the History of Precision Oncology. Surg Oncol Clin N Am. 2020 Jan;29(1):35-49. doi: 10.1016/j.soc.2019.08.003. Epub 2019 Oct 29. PMID: 31757312; PMCID: PMC6878897.

22. Senft D, Leiserson MDM, Ruppin E, Ronai ZA. Precision Oncology: The Road Ahead. Trends Mol Med. 2017 Oct;23(10):874-898. doi: 10.1016/j.molmed.2017.08.003. Epub 2017 Sep 5. PMID: 28887051; PMCID: PMC5718207.

23. Pfohl U, Pflaume A, Regenbrecht M, Finkler S, Graf Adelmann Q, Reinhard C, Regenbrecht CRA, Wedeken L. Precision Oncology Beyond Genomics: The Future Is Here—It Is Just Not Evenly Distributed. Cells. 2021; 10(4):928. https://doi.org/10.3390/cells10040928

24. Song, I.-W.; Vo, H.H.; Chen, Y.-S.; Baysal, M.A.; Kahle, M.; Johnson, A.; Tsimberidou, A.M. Precision Oncology: Evolving Clinical Trials across Tumor Types. Cancers 2023, 15, 1967. https://doi.org/10.3390/cancers15071967

25. Advani D, Sharma S, Kumari S, Ambasta RK, Kumar P. Precision Oncology, Signaling, and Anticancer Agents in Cancer Therapeutics. Anticancer Agents Med Chem. 2022;22(3):433-468. doi: 10.2174/1871520621666210308101029. PMID: 33687887.

26. van Dijk EL, Auger H, Jaszczyszyn Y, Thermes C. Ten years of next-generation sequencing technology. Trends Genet. 2014 Sep;30(9):418-26. doi: 10.1016/j.tig.2014.07.001. Epub 2014 Aug 6. PMID: 25108476.

27. Diacofotaki, Anna, Axelle Loriot, and Charles De Smet. 2022. "Identification of Tissue-Specific Gene Clusters Induced by DNA Demethylation in Lung Adenocarcinoma: More Than Germline Genes" Cancers 14, no. 4: 1007. https://doi.org/10.3390/cancers14041007

28. Jafri, M.A., Ansari, S.A., Alqahtani, M.H. et al. Roles of telomeres and telomerase in cancer,

and advances in telomerase-targeted therapies. Genome Med 8, 69 (2016). https://doi.org/10.1186/s13073-016-0324-x

29. Bielski, C.M., Taylor, B.S. Homing in on genomic instability as a therapeutic target in cancer. Nat Commun 12, 3663 (2021). https://doi.org/10.1038/s41467-021-23965-5

30. Anwar, S.L.; Wulaningsih, W.; Lehmann, U. Transposable Elements in Human Cancer: Causes and Consequences of Deregulation. Int. J. Mol. Sci. 2017, 18, 974. https://doi.org/10.3390/ijms18050974

31. Fox EJ, Prindle MJ, Loeb LA. Do mutator mutations fuel tumorigenesis? Cancer Metastasis Rev. 2013 Dec;32(3-4):353-61. doi: 10.1007/s10555-013-9426-8. PMID: 23592419; PMCID: PMC3987827.

32. Saito, S.; Ku, C.-C.; Wuputra, K.; Pan, J.-B.; Lin, C.-S.; Lin, Y.-C.; Wu, D.-C.; Yokoyama, K.K. Biomarkers of Cancer Stem Cells for Experimental Research and Clinical Application. J.Pers. Med. 2022, 12, 715. https://doi.org/10.3390/jpm12050715

33. Tan, B., Park, C., Ailles, L. et al. The cancer stem cell hypothesis: a work in progress. Lab Invest 86, 1203–1207 (2006). https://doi.org/10.1038/labinvest.3700488

34. Gupta, P.K.; Saraff, M.; Gahtori, R.; Negi, N.; Tripathi, S.K.; Kumar, J.; Kumar, S.; Aldhayan, S.H.; Dhanasekaran, S.; Abomughaid, M.M.; Dua, K.; Gundamaraju, R.; Ojha, S.; Ruokolainen, J.; Jha, N.K.; Kesari, K.K. Phytomedicines Targeting Cancer Stem Cells: Therapeutic Opportunities and Prospects for Pharmaceutical Development. Pharmaceuticals 2021, 14, 676. https://doi.org/10.3390/ph14070676

35. Walcher L, Kistenmacher AK, Suo H, Kitte R, Dluczek S, Strauß A, Blaudszun AR, Yevsa T, Fricke S, Kossatz-Boehlert U. Cancer Stem Cells-Origins and Biomarkers: Perspectives for Targeted Personalized Therapies. Front Immunol. 2020 Aug 7;11:1280. doi: 10.3389/fimmu.2020.01280. PMID: 32849491; PMCID: PMC7426526.

36. Reya, T., Morrison, S., Clarke, M. et al. Stem cells, cancer, and cancer stem cells. Nature 414, 105–111 (2001). https://doi.org/10.1038/35102167

37. Kesh K, Gupta VK, Durden B, Garrido V, Mateo-Victoriano B, Lavania SP, Banerjee S. Therapy Resistance, Cancer Stem Cells and ECM in Cancer: The Matrix Reloaded. Cancers (Basel). 2020 Oct 21;12(10):3067. doi: 10.3390/cancers12103067. PMID: 33096662; PMCID:

PMC7589733.
38. Kulsum S, Raju N, Raghavan N, Ramanjanappa RDR, Sharma A, Mehta A, Kuriakose MA,Suresh A. Cancer stem cells and fibroblast niche cross talk in an in-vitro oral dysplasia model. Mol Carcinog. 2019 May;58(5):820-831. doi: 10.1002/mc.22974. Epub 2019 Jan 31. PMID: 30644602.

39. Dunn GP, Old LJ, Schreiber RD. The immunobiology of cancer immunosurveillance and immunoediting. Immunity. 2004 Aug;21(2):137-48. doi: 10.1016/j.immuni.2004.07.017. PMID: 15308095.

40. Clara JA, Monge C, Yang Y, Takebe N. Targeting signalling pathways and the immune microenvironment of cancer stem cells - a clinical update. Nat Rev Clin Oncol. 2020 Apr;17(4):204-232. doi: 10.1038/s41571-019-0293-2. Epub 2019 Dec 2. PMID: 31792354.

41. Wheeler DA, Wang L. From human genome to cancer genome: the first decade. Genome Res. 2013 Jul;23(7):1054-62. doi: 10.1101/gr.157602.113. PMID: 23817046; PMCID: PMC3698498.

42. Engeland K. Cell cycle regulation: p53-p21-RB signaling. Cell Death Differ. 2022 May;29(5):946-960. doi: 10.1038/s41418-022-00988-z. Epub 2022 Mar 31. PMID: 35361964; PMCID: PMC9090780.

43. Kalkat M, De Melo J, Hickman KA, Lourenco C, Redel C, Resetca D, Tamachi A, Tu WB, Penn LZ. MYC Deregulation in Primary Human Cancers. Genes (Basel). 2017 May 25;8(6):151. doi: 10.3390/genes8060151. PMID: 28587062; PMCID: PMC5485515

44. Metibemu, D.S., Akinloye, O.A., Akamo, A.J. et al. Exploring receptor tyrosine kinases-inhibitors in Cancer treatments. Egypt J Med Hum Genet 20, 35 (2019). https://doi.org/10.1186/s43042-019-0035-0

45. Chaudhary PK, Kim S. An Insight into GPCR and G-Proteins as Cancer Drivers. Cells. 2021 Nov 24;10(12):3288. doi: 10.3390/cells10123288. PMID: 34943797; PMCID: PMC8699078.

46. Prior IA, Lewis PD, Mattos C. A comprehensive survey of Ras mutations in cancer. Cancer Res. 2012 May 15;72(10):2457-67. doi: 10.1158/0008-5472.CAN-11-2612. PMID: 22589270; PMCID: PMC3354961.

47. Vaidya FU, Sufiyan Chhipa A, Mishra V, Gupta VK, Rawat SG, Kumar A, Pathak C.

Molecular and cellular paradigms of multidrug resistance in cancer. Cancer Rep (Hoboken). 2022 Dec;5(12):e1291. doi: 10.1002/cnr2.1291. Epub 2020 Oct 13. PMID: 33052041; PMCID: PMC9780431.

48. Telkoparan-Akillilar P, Panieri E, Cevik D, Suzen S, Saso L. Therapeutic Targeting of the NRF2 Signaling Pathway in Cancer. Molecules. 2021 Mar 5;26(5):1417. doi: 10.3390/molecules26051417. PMID: 33808001; PMCID: PMC7961421.

49. Hua, H., Kong, Q., Yin, J. et al. Insulin-like growth factor receptor signaling in tumorigenesis and drug resistance: a challenge for cancer therapy. J Hematol Oncol 13, 64 (2020). https://doi.org/10.1186/s13045-020-00904-3

50. Su, Z., Yang, Z., Xu, Y. et al. Apoptosis, autophagy, necroptosis, and cancer metastasis. Mol Cancer 14, 48 (2015). https://doi.org/10.1186/s12943-015-0321-5

51. Kaloni D, Diepstraten ST, Strasser A, Kelly GL. BCL-2 protein family: attractive targets for cancer therapy. Apoptosis. 2022 Nov 7. doi: 10.1007/s10495-022-01780-7. Epub ahead of print. PMID: 36342579.

52. Popova, N.V.; Jücker, M. The Functional Role of Extracellular Matrix Proteins in Cancer. Cancers 2022, 14, 238. https://doi.org/10.3390/cancers14010238

53. Kessler T, Hache H, Wierling C. Integrative analysis of cancer-related signaling pathways. Front Physiol. 2013 Jun 4;4:124. doi: 10.3389/fphys.2013.00124. PMID: 23760067; PMCID: PMC3671203.

54. Hanahan D, Weinberg RA. The hallmarks of cancer. Cell. 2000 Jan 7;100(1):57-70. doi: 10.1016/s0092-8674(00)81683-9. PMID: 10647931.

55. Lee EY, Muller WJ. Oncogenes and tumor suppressor genes. Cold Spring Harb Perspect Biol. 2010 Oct;2(10):a003236. doi: 10.1101/cshperspect.a003236. Epub 2010 Aug 18. PMID: 20719876; PMCID: PMC2944361.

56. Orr B, Compton DA. A double-edged sword: how oncogenes and tumor suppressor genes can contribute to chromosomal instability. Front Oncol. 2013 Jun 27;3:164. doi: 10.3389/fonc.2013.00164. PMID: 23825799; PMCID: PMC3695391.

57. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011 Mar

4;144(5):646-74. doi: 10.1016/j.cell.2011.02.013. PMID: 21376230.

58. Hanahan D. Hallmarks of Cancer: New Dimensions. Cancer Discov. 2022 Jan;12(1):31-46. doi: 10.1158/2159-8290.CD-21-1059. PMID: 35022204.

59. Adjei AA, Hidalgo M. Intracellular signal transduction pathway proteins as targets for cancer therapy. J Clin Oncol. 2005 Aug 10;23(23):5386-403. doi: 10.1200/JCO.2005.23.648. Epub 2005 Jun 27. PMID: 15983388.

60. Bayat Mokhtari R, Homayouni TS, Baluch N, Morgatskaya E, Kumar S, Das B, Yeger H. Combination therapy in combating cancer. Oncotarget. 2017 Jun 6;8(23):38022-38043. doi: 10.18632/oncotarget.16723. PMID: 28410237; PMCID: PMC5514969.

61.Sever R, Brugge JS. Signal transduction in cancer. Cold Spring Harb Perspect Med. 2015 Apr1;5(4):a006098. doi: 10.1101/cshperspect.a006098. PMID: 25833940; PMCID: PMC4382731.

62.Dillon M, Lopez A, Lin E, Sales D, Perets R, Jain P. Progress on Ras/MAPK Signaling Research and Targeting in Blood and Solid Cancers. Cancers. 2021; 13(20):5059. https://doi.org/10.3390/cancers13205059

63. Santarpia L, Lippman SM, El-Naggar AK. Targeting the MAPK-RAS-RAF signaling pathway in cancer therapy. Expert Opin Ther Targets. 2012 Jan;16(1):103-19. doi: 10.1517/14728222.2011.645805. Epub 2012 Jan 12. PMID: 22239440; PMCID: PMC3457779.

64. Hua, H., Kong, Q., Zhang, H. et al. Targeting mTOR for cancer therapy. J Hematol Oncol 12, 71 (2019). https://doi.org/10.1186/s13045-019-0754-1

65. Yang, J., Nie, J., Ma, X. et al. Targeting PI3K in cancer: mechanisms and advances in clinical trials. Mol Cancer 18, 26 (2019). https://doi.org/10.1186/s12943-019-0954-x

66. Papa A, Pandolfi PP. The PTEN⁻PI3K Axis in Cancer. Biomolecules. 2019 Apr 17;9(4):153. doi: 10.3390/biom9040153. PMID: 30999672; PMCID: PMC6523724.

67. Alzahrani AS. PI3K/Akt/mTOR inhibitors in cancer: At the bench and bedside. Semin Cancer Biol. 2019 Dec;59:125-132. doi: 10.1016/j.semcancer.2019.07.009. Epub 2019 Jul 16.

PMID: 31323288.

68. Brooks AJ, Putoczki T. JAK-STAT Signalling Pathway in Cancer. Cancers (Basel). 2020 Jul 20;12(7):1971. doi: 10.3390/cancers12071971. PMID: 32698360; PMCID: PMC7409105.

69. Thomas, S., Snowden, J., Zeidler, M. et al. The role of JAK/STAT signalling in the pathogenesis, prognosis and treatment of solid tumours. Br J Cancer 113, 365–371 (2015). https://doi.org/10.1038/bjc.2015.233

70. Loh CY, Arya A, Naema AF, Wong WF, Sethi G, Looi CY. Signal Transducer and Activator of Transcription (STATs) Proteins in Cancer and Inflammation: Functions and Therapeutic Implication. Front Oncol. 2019 Feb 21;9:48. doi: 10.3389/fonc.2019.00048. PMID: 30847297; PMCID: PMC6393348.

71. Owen KL, Brockwell NK, Parker BS. JAK-STAT Signaling: A Double-Edged Sword of Immune Regulation and Cancer Progression. Cancers (Basel). 2019 Dec 12;11(12):2002. doi: 10.3390/cancers11122002. PMID: 31842362; PMCID: PMC6966445.

72. Rah B, Rather RA, Bhat GR, Baba AB, Mushtaq I, Farooq M, Yousuf T, Dar SB, Parveen S, Hassan R, Mohammad F, Qassim I, Bhat A, Ali S, Zargar MH, Afroze D. JAK/STAT Signaling: Molecular Targets, Therapeutic Opportunities, and Limitations of Targeted Inhibitions in Solid Malignancies. Front Pharmacol. 2022 Mar 24;13:821344. doi: 10.3389/fphar.2022.821344. PMID: 35401182; PMCID: PMC8987160.

73. Zhao M, Mishra L, Deng CX. The role of TGF-β/SMAD4 signaling in cancer. Int J Biol Sci. 2018 Jan 12;14(2):111-123. doi: 10.7150/ijbs.23230. PMID: 29483830; PMCID: PMC5821033.

74. Samanta D, Datta PK. Alterations in the Smad pathway in human cancers. Front Biosci (Landmark Ed). 2012 Jan 1;17(4):1281-93. doi: 10.2741/3986. PMID: 22201803; PMCID: PMC4281477.

75. Akhurst RJ. Targeting TGF-β Signaling for Therapeutic Gain. Cold Spring Harb Perspect Biol. 2017 Oct 3;9(10):a022301. doi: 10.1101/cshperspect.a022301. PMID: 28246179; PMCID: PMC5630004.

76. Huang CY, Chung CL, Hu TH, Chen JJ, Liu PF, Chen CL. Recent progress in TGF-β inhibitors for cancer therapy. Biomed Pharmacother. 2021 Feb;134:111046. doi: 10.1016/j.biopha.2020.111046. Epub 2020 Dec 16. PMID: 33341049.

77. Han, Y. Analysis of the role of the Hippo pathway in cancer. J Transl Med 17, 116 (2019). https://doi.org/10.1186/s12967-019-1869-4

78. Cunningham R, Hansen CG. The Hippo pathway in cancer: YAP/TAZ and TEAD as therapeutic targets in cancer. Clin Sci (Lond). 2022 Feb 11;136(3):197-222. doi: 10.1042/CS20201474. PMID: 35119068; PMCID: PMC8819670.

79. Calses PC, Crawford JJ, Lill JR, Dey A. Hippo Pathway in Cancer: Aberrant Regulation and Therapeutic Opportunities. Trends Cancer. 2019 May;5(5):297-307. doi:10.1016/j.trecan.2019.04.001. Epub 2019 May 16. PMID: 31174842.

80. Zhan, T., Rindtorff, N. & Boutros, M. Wnt signaling in cancer. Oncogene 36, 1461–1473 (2017). https://doi.org/10.1038/onc.2016.304

81. Martin-Orozco E, Sanchez-Fernandez A, Ortiz-Parra I, Ayala-San Nicolas M. WNT Signaling in Tumors: The Way to Evade Drugs and Immunity. Front Immunol. 2019 Dec 20;10:2854. doi: 10.3389/fimmu.2019.02854. PMID: 31921125; PMCID: PMC6934036.

82. Zhang, Y., Wang, X. Targeting the Wnt/β-catenin signaling pathway in cancer. J Hematol Oncol 13, 165 (2020). https://doi.org/10.1186/s13045-020-00990-3

83. Skoda AM, Simovic D, Karin V, Kardum V, Vranic S, Serman L. The role of the Hedgehog signaling pathway in cancer: A comprehensive review. Bosn J Basic Med Sci. 2018 Feb 20;18(1):8-20. doi: 10.17305/bjbms.2018.2756. PMID: 29274272; PMCID: PMC5826678.

84. Kumar V, Vashishta M, Kong L, Wu X, Lu JJ, Guha C, Dwarakanath BS. The Role of Notch, Hedgehog, and Wnt Signaling Pathways in the Resistance of Tumors to Anticancer Therapies. Front Cell Dev Biol. 2021 Apr 22;9:650772. doi: 10.3389/fcell.2021.650772. PMID: 33968932; PMCID: PMC8100510.

85. Chang, W.H., Lai, A.G. Aberrations in Notch-Hedgehog signalling reveal cancer stem cells harbouring conserved oncogenic properties associated with hypoxia and immunoevasion. Br J

Cancer 121, 666–678 (2019). https://doi.org/10.1038/s41416-019-0572-9

86. Shibata M, Hoque MO. Targeting Cancer Stem Cells: A Strategy for Effective Eradication of Cancer. Cancers. 2019; 11(5):732. https://doi.org/10.3390/cancers11050732

87. Yang, L., Shi, P., Zhao, G. et al. Targeting cancer stem cell pathways for cancer therapy. Sig Transduct Target Ther 5, 8 (2020). https://doi.org/10.1038/s41392-020-0110-5

88. Shih, VS., Tsui, R., Caldwell, A. et al. A single NFκB system for both canonical and non-canonical signaling. Cell Res 21, 86–102 (2011). https://doi.org/10.1038/cr.2010.161

89. Hoesel, B., Schmid, J.A. The complexity of NF-κB signaling in inflammation and cancer. Mol Cancer 12, 86 (2013). https://doi.org/10.1186/1476-4598-12-86

90. Huber MA, Beug H, Wirth T. Epithelial-mesenchymal transition: NF-kappaB takes center stage. Cell Cycle. 2004 Dec;3(12):1477-80. doi: 10.4161/cc.3.12.1280. Epub 2004 Dec 4. PMID: 15539952.

91. Fonseca LC, Dadarkar SS, Lobo AS, Mishra PB, Thakkar AD, Chandrababu S, Padigaru M. NF-κB-mediated anti-inflammatory activity of the sesquiterpene lactone 7-hydroxyfrullanolide. Eur J Pharmacol. 2011 Apr 25;657(1-3):41-50. doi: 10.1016/j.ejphar.2011.01.050. Epub 2011 Feb 4. PMID: 21296061.

92. Oeckinghaus, A., Hayden, M. & Ghosh, S. Crosstalk in NF-κB signaling pathways. Nat Immunol 12, 695–708 (2011). https://doi.org/10.1038/ni.2065

93. Luo JL, Kamata H, Karin M. IKK/NF-kappaB signaling: balancing life and death--a new approach to cancer therapy. J Clin Invest. 2005 Oct;115(10):2625-32. doi: 10.1172/JCI26322. PMID: 16200195; PMCID: PMC1236696.

94. Erstad DJ, Cusack JC Jr. Targeting the NF-κB pathway in cancer therapy. Surg Oncol Clin N Am. 2013 Oct;22(4):705-46. doi: 10.1016/j.soc.2013.06.011. Epub 2013 Aug 6. PMID: 24012396.

95. Hoong BYD, Gan YH, Liu H, Chen ES. cGAS-STING pathway in oncogenesis and cancer therapeutics. Oncotarget. 2020 Jul 28;11(30):2930-2955. doi: 10.18632/oncotarget.27673. PMID: 32774773; PMCID: PMC7392626.

96. Khoo LT, Chen LY. Role of the cGAS-STING pathway in cancer development and oncotherapeutic approaches. EMBO Rep. 2018 Dec;19(12):e46935. doi: 10.15252/embr.201846935. Epub 2018 Nov 16. PMID: 30446584; PMCID: PMC6280650.

97. Jiang, M., Chen, P., Wang, L. et al. cGAS-STING, an important pathway in cancer immunotherapy. J Hematol Oncol 13, 81 (2020). https://doi.org/10.1186/s13045-020-00916-z

98. Kümper S, Mardakheh FK, McCarthy A, Yeo M, Stamp GW, Paul A, Worboys J, Sadok A, Jørgensen C, Guichard S, Marshall CJ. Rho-associated kinase (ROCK) function is essential for cell cycle progression, senescence and tumorigenesis. Elife. 2016 Jan 14;5:e12994. doi: 10.7554/eLife.12203. PMID: 26765561; PMCID: PMC4798951.

99. Kim S, Kim SA, Han J, Kim IS. Rho-Kinase as a Target for Cancer Therapy and Its Immunotherapeutic Potential. Int J Mol Sci. 2021 Nov 29;22(23):12916. doi: 10.3390/ijms222312916. PMID: 34884721; PMCID: PMC8657458.

100. Ohashi H, Hasegawa M, Wakimoto K, Miyamoto-Sato E. Next-generation technologies for multiomics approaches including interactome sequencing. Biomed Res Int. 2015;2015:104209. doi: 10.1155/2015/104209. Epub 2015 Jan 12. PMID: 25649523; PMCID: PMC4306365.

101. Heo YJ, Hwa C, Lee GH, Park JM, An JY. Integrative Multi-Omics Approaches in Cancer Research: From Biological Networks to Clinical Subtypes. Mol Cells. 2021 Jul 31;44(7):433-443. doi: 10.14348/molcells.2021.0042. PMID: 34238766; PMCID: PMC8334347.

102. Ding MQ, Chen L, Cooper GF, Young JD, Lu X. Precision Oncology beyond Targeted Therapy: Combining Omics Data with Machine Learning Matches the Majority of Cancer Cells to Effective Therapeutics. Mol Cancer Res. 2018 Feb;16(2):269-278. doi: 10.1158/1541-7786.MCR-17-0378. Epub 2017 Nov 13. PMID: 29133589; PMCID: PMC5821274.

103. Nicora G, Vitali F, Dagliati A, Geifman N, Bellazzi R. Integrated Multi-Omics Analyses in Oncology: A Review of Machine Learning Methods and Tools. Front Oncol. 2020 Jun 30;10:1030. doi: 10.3389/fonc.2020.01030. PMID: 32695678; PMCID: PMC7338582.

104. Erickson BJ. Basic Artificial Intelligence Techniques: Machine Learning and Deep

Learning. Radiologic Clinics of North America. 2021 Nov;59(6):933-940. DOI: 10.1016/j.rcl.2021.06.004. PMID: 34689878.

105. Lee, DonHee, and Seong No Yoon. 2021. "Application of Artificial Intelligence-Based Technologies in the Healthcare Industry: Opportunities and Challenges" International Journal of Environmental Research and Public Health 18, no. 1: 271. https://doi.org/10.3390/ijerph18010271

106. Filipp, F.V. Opportunities for Artificial Intelligence in Advancing Precision Medicine. Curr Genet Med Rep 7, 208–213 (2019). https://doi.org/10.1007/s40142-019-00177-4

107. Azuaje, F. Artificial intelligence for precision oncology: beyond patient stratification. npj Precision Onc 3, 6 (2019). https://doi.org/10.1038/s41698-019-0078-1

108. Deng C, Ji X, Rainey C, Zhang J, Lu W. Integrating Machine Learning with Human Knowledge. iScience. 2020 Oct 9;23(11):101656. doi: 10.1016/j.isci.2020.101656. PMID: 33134890; PMCID: PMC7588855.

109. Shimizu H, Nakayama KI. Artificial intelligence in oncology. Cancer Sci. 2020 May;111(5):1452-1460. doi: 10.1111/cas.14377. Epub 2020 Mar 21. PMID: 32133724; PMCID: PMC7226189.

110. Adam, G., Rampášek, L., Safikhani, Z. et al. Machine learning approaches to drug response prediction: challenges and recent progress. npj Precis. Onc. 4, 19 (2020).

111. Kuenzi BM, Park J, Fong SH, Sanchez KS, Lee J, Kreisberg JF, Ma J, Ideker T. Predicting Drug Response and Synergy Using a Deep Learning Model of Human Cancer Cells. Cancer Cell. 2020 Nov 9;38(5):672-684.e6. doi: 10.1016/j.ccell.2020.09.014. Epub 2020 Oct 22. PMID: 33096023; PMCID: PMC7737474.

112. Jumper, J., Evans, R., Pritzel, A. et al. Highly accurate protein structure prediction with AlphaFold. Nature 596, 583–589 (2021). https://doi.org/10.1038/s41586-021-03819-2

113. Thornton, J.M., Laskowski, R.A. & Borkakoti, N. AlphaFold heralds a data-driven revolution in biology and medicine. Nat Med 27, 1666–1669 (2021). https://doi.org/10.1038/s41591-021-01533-0

114. Bera K, Schalper KA, Rimm DL, Velcheti V, Madabhushi A. Artificial intelligence in

digital pathology - new tools for diagnosis and precision oncology. Nat Rev Clin Oncol. 2019 Nov;16(11):703-715. doi: 10.1038/s41571-019-0252-y. Epub 2019 Aug 9. PMID: 31399699; PMCID: PMC6880861.
115. Cancer Genome Atlas Research Network, Weinstein JN, Collisson EA, Mills GB, Shaw KR, Ozenberger BA, Ellrott K, Shmulevich I, Sander C, Stuart JM. The Cancer Genome Atlas Pan-Cancer analysis project. Nat Genet. 2013 Oct;45(10):1113-20. doi: 10.1038/ng.2764. PMID: 24071849; PMCID: PMC3919969.

116. Tomczak K, Czerwińska P, Wiznerowicz M. The Cancer Genome Atlas (TCGA): an immeasurable source of knowledge. Contemp Oncol (Pozn). 2015;19(1A):A68-77. doi: 10.5114/wo.2014.47136. PMID: 25691825; PMCID: PMC4322527.

117. Chakravarty D, Gao J, Phillips SM, Kundra R, Zhang H, Wang J, Rudolph JE, Yaeger R, Soumerai T, Nissan MH, Chang MT, Chandarlapaty S, Traina TA, Paik PK, Ho AL, Hantash FM, Grupe A, Baxi SS, Callahan MK, Snyder A, Chi P, Danila D, Gounder M, Harding JJ, Hellmann MD, Iyer G, Janjigian Y, Kaley T, Levine DA, Lowery M, Omuro A, Postow MA, Rathkopf D, Shoushtari AN, Shukla N, Voss M, Paraiso E, Zehir A, Berger MF, Taylor BS, Saltz LB, Riely GJ, Ladanyi M, Hyman DM, Baselga J, Sabbatini P, Solit DB, Schultz N. OncoKB: A Precision Oncology Knowledge Base. JCO Precis Oncol. 2017 Jul;2017:PO.17.00011. doi: 10.1200/PO.17.00011. Epub 2017 May 16. PMID: 28890946; PMCID: PMC5586540.

118. Pallarz S, Benary M, Lamping M, Rieke D, Starlinger J, Sers C, Wiegandt DL, Seibert M, Ševa J, Schäfer R, Keilholz U, Leser U. Comparative Analysis of Public Knowledge Bases for Precision Oncology. JCO Precis Oncol. 2019 Jul 24;3:PO.18.00371. doi: 10.1200/PO.18.00371. PMID: 32914021; PMCID: PMC7446431.

119. Chandran UR, Medvedeva OP, Barmada MM, Blood PD, Chakka A, Luthra S, Ferreira A, Wong KF, Lee AV, Zhang Z, Budden R, Scott JR, Berndt A, Berg JM, Jacobson RS. TCGA Expedition: A Data Acquisition and Management System for TCGA Data. PLoS One. 2016 Oct 27;11(10):e0165395. doi: 10.1371/journal.pone.0165395. PMID: 27788220; PMCID: PMC5082933.

120. Tatlow, P., Piccolo, S. A cloud-based workflow to quantify transcript-expression levels in public cancer compendia. Sci Rep 6, 39259 (2016). https://doi.org/10.1038/srep39259

121. Li, Y., Kang, K., Krahn, J.M. et al. A comprehensive genomic pan-cancer classification using The Cancer Genome Atlas gene expression data. BMC Genomics 18, 508 (2017). https://doi.org/10.1186/s12864-017-3906-0

122. Cooper LA, Demicco EG, Saltz JH, Powell RT, Rao A, Lazar AJ. PanCancer insights from The Cancer Genome Atlas: the pathologist's perspective. J Pathol. 2018 Apr;244(5):512-524. doi: 10.1002/path.5028. Epub 2018 Feb 22. PMID: 29288495; PMCID: PMC6240356.
123. Hoadley KA, Yau C, Wolf DM, Cherniack AD, Tamborero D, Ng S, Leiserson MDM, Niu B, McLellan MD, Uzunangelov V, Zhang J, Kandoth C, Akbani R, Shen H, Omberg L, Chu A, Margolin AA, Van't Veer LJ, Lopez-Bigas N, Laird PW, Raphael BJ, Ding L, Robertson AG, Byers LA, Mills GB, Weinstein JN, Van Waes C, Chen Z, Collisson EA; Cancer Genome Atlas Research Network, Benz CC, Perou CM, Stuart JM. Multiplatform analysis of 12 cancer types reveals molecular classification within and across tissues of origin. Cell. 2014 Aug 14;158(4):929-944. doi: 10.1016/j.cell.2014.06.049. Epub 2014 Aug 7. PMID: 25109877; PMCID: PMC4152462.

124. Hoadley KA, Yau C, Hinoue T, Wolf DM, Lazar AJ, Drill E, Shen R, Taylor AM, Cherniack AD, Thorsson V, Akbani R, Bowlby R, Wong CK, Wiznerowicz M, Sanchez-Vega F, Robertson AG, Schneider BG, Lawrence MS, Noushmehr H, Malta TM; Cancer Genome Atlas Network, Stuart JM, Benz CC, Laird PW. Cell-of-Origin Patterns Dominate the Molecular Classification of 10,000 Tumors from 33 Types of Cancer. Cell. 2018 Apr 5;173(2):291-304.e6. doi: 10.1016/j.cell.2018.03.022. PMID: 29625048; PMCID: PMC5957518.

125. Sanchez-Vega F, Mina M, Armenia J, Chatila WK, Luna A, La KC, Dimitriadoy S, Liu DL, Kantheti HS, Saghafinia S, Chakravarty D, Daian F, Gao Q, Bailey MH, Liang WW, Foltz SM, Shmulevich I, Ding L, Heins Z, Ochoa A, Gross B, Gao J, Zhang H, Kundra R, Kandoth C, Bahceci I, Dervishi L, Dogrusoz U, Zhou W, Shen H, Laird PW, Way GP, Greene CS, Liang H, Xiao Y, Wang C, Iavarone A, Berger AH, Bivona TG, Lazar AJ, Hammer GD, Giordano T, Kwong LN, McArthur G, Huang C, Tward AD, Frederick MJ, McCormick F, Meyerson M; Cancer Genome Atlas Research Network, Van Allen EM, Cherniack AD, Ciriello G, Sander C, Schultz N. Oncogenic Signaling Pathways in The Cancer Genome Atlas. Cell. 2018 Apr 5;173(2):321-337.e10. doi: 10.1016/j.cell.2018.03.035. PMID: 29625050; PMCID: PMC6070353.

126. Wang E, Zaman N, Mcgee S, Milanese JS, Masoudi-Nejad A, O'Connor-McCourt M. Predictive genomics: a cancer hallmark network framework for predicting tumor clinical phenotypes using genome sequencing data. Semin Cancer Biol. 2015 Feb;30:4-12. doi: 10.1016/j.semcancer.2014.04.002. Epub 2014 Apr 18. PMID: 24747696.

127. Wang E. Understanding genomic alterations in cancer genomes using an integrative network approach. Cancer Lett. 2013 Nov 1;340(2):261-9. doi: 10.1016/j.canlet.2012.11.050. Epub 2012 Dec 22. PMID: 23266571.

128. Krogan NJ, Lippman S, Agard DA, Ashworth A, Ideker T. The cancer cell map initiative: defining the hallmark networks of cancer. Mol Cell. 2015 May 21;58(4):690-8. doi:

10.1016/j.molcel.2015.05.008. PMID: 26000852; PMCID: PMC5359018.

129. Ghandi M, Huang FW, Jané-Valbuena J, Kryukov GV, Lo CC, McDonald ER 3rd, Barretina J, Gelfand ET, Bielski CM, Li H, Hu K, Andreev-Drakhlin AY, Kim J, Hess JM, Haas BJ, Aguet F, Weir BA, Rothberg MV, Paolella BR, Lawrence MS, Akbani R, Lu Y, Tiv HL, Gokhale PC, de Weck A, Mansour AA, Oh C, Shih J, Hadi K, Rosen Y, Bistline J, Venkatesan K, Reddy A, Sonkin D, Liu M, Lehar J, Korn JM, Porter DA, Jones MD, Golji J, Caponigro G, Taylor JE, Dunning CM, Creech AL, Warren AC, McFarland JM, Zamanighomi M, Kauffmann A, Stransky N, Imielinski M, Maruvka YE, Cherniack AD, Tsherniak A, Vazquez F, Jaffe JD, Lane AA, Weinstock DM, Johannessen CM, Morrissey MP, Stegmeier F, Schlegel R, Hahn WC, Getz G, Mills GB, Boehm JS, Golub TR, Garraway LA, Sellers WR. Next-generation characterization of the Cancer Cell Line Encyclopedia. Nature. 2019 May;569(7757):503-508. doi: 10.1038/s41586-019-1186-3. Epub 2019 May 8. PMID: 31068700; PMCID: PMC6697103.

130. Junker JP, van Oudenaarden A. Every cell is special: genome-wide studies add a new dimension to single-cell biology. Cell. 2014 Mar 27;157(1):8-11. doi: 10.1016/j.cell.2014.02.010. PMID: 24679522.

131. Reddy RB, Khora SS, Suresh A. Molecular prognosticators in clinically and pathologically distinct cohorts of head and neck squamous cell carcinoma-A meta-analysis approach. PLoS One. 2019 Jul 16;14(7):e0218989. doi: 10.1371/journal.pone.0218989. PMID: 31310629; PMCID: PMC6634788.

132. Saadatpour A, Lai S, Guo G, Yuan GC. Single-Cell Analysis in Cancer Genomics. Trends Genet. 2015 Oct;31(10):576-586. doi: 10.1016/j.tig.2015.07.003. PMID: 26450340; PMCID: PMC5282606.

133. Lim, ZF., Ma, P.C. Emerging insights of tumor heterogeneity and drug resistance mechanisms in lung cancer targeted therapy. J Hematol Oncol 12, 134 (2019). https://doi.org/10.1186/s13045-019-0818-2

134. Dagogo-Jack, I., Shaw, A. Tumour heterogeneity and resistance to cancer therapies. Nat Rev Clin Oncol 15, 81–94 (2018). https://doi.org/10.1038/nrclinonc.2017.166

135. Hong, T.H., Park, WY. Single-cell genomics technology: perspectives. Exp Mol Med 52, 1407–1408 (2020). https://doi.org/10.1038/s12276-020-00495-6

136. Hu P, Zhang W, Xin H, Deng G. Single Cell Isolation and Analysis. Front Cell Dev Biol. 2016 Oct 25;4:116. doi: 10.3389/fcell.2016.00116. PMID: 27826548; PMCID: PMC5078503.

137. Yang Y, Xu J, Ge S, Lai L. CRISPR/Cas: Advances, Limitations, and Applications for Precision Cancer Research. Front Med (Lausanne). 2021 Mar 3;8:649896. doi: 10.3389/fmed.2021.649896. PMID: 33748164; PMCID: PMC7965951.

138. Di Palma S, Bodenmiller B. Unraveling cell populations in tumors by single-cell mass cytometry. Curr Opin Biotechnol. 2015 Feb;31:122-9. doi: 10.1016/j.copbio.2014.07.004. Epub 2014 Aug 11. PMID: 25123841.

139. Guo M, Peng Y, Gao A, Du C, Herman JG. Epigenetic heterogeneity in cancer. Biomark Res. 2019 Oct 31;7:23. doi: 10.1186/s40364-019-0174-y. PMID: 31695915; PMCID: PMC6824025.

140. Yuan Y. Spatial Heterogeneity in the Tumor Microenvironment. Cold Spring Harb Perspect Med. 2016 Aug 1;6(8):a026583. doi: 10.1101/cshperspect.a026583. PMID: 27481837; PMCID: PMC4968167.

141. Brady, L., Kriner, M., Coleman, I. et al. Inter- and intra-tumor heterogeneity of metastatic prostate cancer determined by digital spatial gene expression profiling. Nat Commun 12, 1426 (2021). https://doi.org/10.1038/s41467-021-21615-4

142. Levy-Jurgenson, A., Tekpli, X., Kristensen, V.N. et al. Spatial transcriptomics inferred from pathology whole-slide images links tumor heterogeneity to survival in breast and lung cancer. Sci Rep 10, 18802 (2020). https://doi.org/10.1038/s41598-020-75708-z

143. Ye F, Huang W, Guo G. Studying hematopoiesis using single-cell technologies. J Hematol Oncol. 2017 Jan 21;10(1):27. doi: 10.1186/s13045-017-0401-7. PMID: 28109325; PMCID: PMC5251333.

144. Zheng, B., Fang, L. Spatially resolved transcriptomics provide a new method for cancer research. J Exp Clin Cancer Res 41, 179 (2022). https://doi.org/10.1186/s13046-022-02385-3

145. Xu, Y., Su, GH., Ma, D. et al. Technological advances in cancer immunity: from immunogenomics to single-cell analysis and artificial intelligence. Sig Transduct Target Ther 6, 312 (2021). https://doi.org/10.1038/s41392-021-00729-7

146. Liotta L, Petricoin E. Molecular profiling of human cancer. Nat Rev Genet. 2000 Oct;1(1):48-56. doi: 10.1038/35049567. PMID: 11262874.

147. Karagiannakos A, Adamaki M, Tsintarakis A, Vojtesek B, Fåhraeus R, Zoumpourlis V, Karakostis K. Targeting Oncogenic Pathways in the Era of Personalized Oncology: A Systemic Analysis Reveals Highly Mutated Signaling Pathways in Cancer Patients and Potential Therapeutic Targets. Cancers (Basel). 2022 Jan 28;14(3):664. doi: 10.3390/cancers14030664. PMID: 35158934; PMCID: PMC8833388.

148. Te Beek ET, Teunissen JJM, Postema JWA, Lafeber A, Ten Broek MRJ. Precision medicine and theranostics using radiopharmaceuticals in oncology. Br J Clin Pharmacol. 2022 Jan;88(1):359-361. doi: 10.1111/bcp.14942. Epub 2021 Jun 22. PMID: 34159632.

149. Zahavi D, Weiner L. Monoclonal Antibodies in Cancer Therapy. Antibodies (Basel). 2020 Jul 20;9(3):34. doi: 10.3390/antib9030034. PMID: 32698317; PMCID: PMC7551545.

150. Lord CJ, Ashworth A. PARP inhibitors: Synthetic lethality in the clinic. Science. 2017 Mar 17;355(6330):1152-1158. doi: 10.1126/science.aam7344. Epub 2017 Mar 16. PMID: 28302823; PMCID: PMC6175050.

151. Slade D. PARP and PARG inhibitors in cancer treatment. Genes Dev. 2020 Mar 1;34(5-6):360-394. doi: 10.1101/gad.334516.119. Epub 2020 Feb 6. PMID: 32029455; PMCID: PMC7050487.

152. Rossi JF, Céballos P, Lu ZY. Immune precision medicine for cancer: a novel insight based on the efficiency of immune effector cells. Cancer Commun (Lond). 2019 Jun 14;39(1):34. doi: 10.1186/s40880-019-0379-3. PMID: 31200766; PMCID: PMC6567551.

153. Pfohl, U.; Pflaume, A.; Regenbrecht, M.; Finkler, S.; Graf Adelmann, Q.; Reinhard, C.; Regenbrecht, C.R.A.; Wedeken, L. Precision Oncology Beyond Genomics: The Future Is Here—It Is Just Not Evenly Distributed. Cells 2021, 10, 928. https://doi.org/10.3390/cells10040928

154. Baghban, R., Roshangar, L., Jahanban-Esfahlan, R. et al. Tumor microenvironment complexity and therapeutic implications at a glance. Cell Commun Signal 18, 59 (2020). https://doi.org/10.1186/s12964-020-0530-4

155. Kareva I. A Combination of Immune Checkpoint Inhibition with Metronomic Chemotherapy as a Way of Targeting Therapy-Resistant Cancer Cells. International Journal of

Molecular Sciences. 2017; 18(10):2134. https://doi.org/10.3390/ijms18102134

156. Chen G, Bodogai M, Tamehiro N, Shen C, Dou J. Cancer Immunotherapy: Theory and Application. J Immunol Res. 2018 Jun 21;2018:7502161. doi: 10.1155/2018/7502161. PMID: 30035133; PMCID: PMC6033242.

157. Kiyotani K, Toyoshima Y, Nakamura Y. Personalized immunotherapy in cancer precision medicine. Cancer Biol Med. 2021 Aug 9;18(4):955–65. doi: 10.20892/j.issn.2095-3941.2021.0032. Epub ahead of print. PMID: 34369137; PMCID: PMC8610159.

158. Zhao, B.; Chen, S.; Hong, Y.; Jia, L.; Zhou, Y.; He, X.; Wang, Y.; Tian, Z.; Yang, Z.; Gao, D. Research Progress of Conjugated Nanomedicine for Cancer Treatment. Pharmaceutics 2022,14, 1522. https://doi.org/10.3390/pharmaceutics14071522

159. Yao Y, Zhou Y, Liu L, Xu Y, Chen Q, Wang Y, Wu S, Deng Y, Zhang J, Shao A. Nanoparticle-Based Drug Delivery in Cancer Therapy and Its Role in Overcoming Drug Resistance. Front Mol Biosci. 2020 Aug 20;7:193. doi: 10.3389/fmolb.2020.00193. PMID: 32974385; PMCID: PMC7468194.

160. Dupont CA, Riegel K, Pompaiah M, Juhl H, Rajalingam K. Druggable genome and precision medicine in cancer: current challenges. FEBS J. 2021 Nov;288(21):6142-6158. doi: 10.1111/febs.15788. Epub 2021 Mar 19. PMID: 33626231.

161. Pereira M.A. et al. (2020). Cancer Genomics in Precision Oncology: Applications, Challenges, and Prospects. In: Masood, N., Shakil Malik, S. (eds) 'Essentials of Cancer Genomic, Computational Approaches and Precision Medicine. Springer, Singapore. https://doi.org/10.1007/978-981-15-1067-0_21

162. Pantziarka P, Bouche G, André N. "Hard" Drug Repurposing for Precision Oncology: The Missing Link? Front Pharmacol. 2018 Jun 14;9:637. doi: 10.3389/fphar.2018.00637. PMID: 29962954; PMCID: PMC6010551.

163. Oprea TI, Bauman JE, Bologa CG, Buranda T, Chigaev A, Edwards BS, Jarvik JW, Gresham HD, Haynes MK, Hjelle B, Hromas R, Hudson L, Mackenzie DA, Muller CY, Reed JC, Simons PC, Smagley Y, Strouse J, Surviladze Z, Thompson T, Ursu O, Waller A, Wandinger-Ness A, Winter SS, Wu Y, Young SM, Larson RS, Willman C, Sklar LA. Drug Repurposing from an Academic Perspective. Drug Discov Today, Ther Strateg. 2011 Winter;8(3-4):61-69. doi: 10.1016/j.ddstr.2011.10.002. PMID: 22368688; PMCID: PMC3285382.

164. Yip HYK, Papa A. Signaling Pathways in Cancer: Therapeutic Targets, Combinatorial Treatments, and New Developments. Cells. 2021 Mar 16;10(3):659. doi: 10.3390/cells10030659. PMID: 33809714; PMCID: PMC8002322.

165. Dugger SA, Platt A, Goldstein DB. Drug development in the era of precision medicine. Nat Rev Drug Discov. 2018 Mar;17(3):183-196. doi: 10.1038/nrd.2017.226. Epub 2017 Dec 8. PMID: 29217837; PMCID: PMC6287751.

Supplementary File 1: New FDA-Approved Oncology Drugs (2021–2022) (https://ascopost.com/issues/june-3-2022-narratives-special-issue/new-fda-approved-oncology-drugs-2021-2022/#.ZDUJRrQ2lAE.)

Supplementary File 2: Ongoing/Cancer Accelerated Approvals (https://www.fda.gov/drugs/resources-information-approved-drugs/ongoing-cancer-accelerated- approvals)