JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

Targeting kinase in cancer treatment

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Abstract : Cancer can be considered as a group of diseases characterized by abnormal cell growth, the ability to invade neighboring tissues and even distant organs, and the possible death of the affected patient if the tumor has progressed beyond what is possible. Cancer treatment includes chemotherapy, gene therapy, surgery, radiation therapy, and a combination of these depending on the severity of the disease. A small molecule kinase inhibitor has recently been successfully demonstrated in the clinical treatment of cancer. Since the first protein kinase exposure in the early 1980s, 37 kinases have been inhibited or received FDA approval for the treatment of breast and lung cancer, with up to 150 kinase-targeted drugs and many kinase-specific inhibitors in clinical phase trials. is in the preclinical phase of drug development. By 2023, 80 FDA-approved small molecule protein kinase inhibitors. This review provides an overview of kinase targeted drugs and outlines the challenges and future opportunities for kinase targeted cancer therapy.

IndexTerms **- Kinase inhibitors, Targeted therapy, Cancer treatment, Signal transduction pathways.**

I. INTRODUCTION

The increasing number of new cancer diagnoses and cancer related deaths worldwide indicates that cancer is a serious threat to public health. Key obstacles to achieving equitable cancer care are highlighted by the disparate cancer burden based on a nation's sociodemographic index (SDI), which is a compoundsite measure of social and economic development that takes into account factors like average years of education, total fertility rate ffor people under 25, and income per capita.The average years of education and the overall fertility rate for individuals under 25 years of age show significant obstacles to reaching global health equality worldwide parity in health.

A broad overview of the worldwide burden of cancer is provided by the following instances.

1) Tracheal, bronchus, and lung cancers are the leading causes of cancer deaths.
2) Breast cancer is the leading cause of cancer-related deaths among women.
3) Diagnoses and deaths from colorectal cancer more than doubled over the past three decades.
4) Liver cancer is among the top five causes of cancer death in 90 countries: the number of new cases per year is predicted to increase by 55 percent between 2020 and 2040.
5) Six percent of new cervical cancer cases 8 in 2018 were diagnosed in women living with HIV and five percent were attributable to the HIV infection, Eighty-five percent of women with cervical cancer and HIV live in sub-Saharan Africa.

The need for new therapies –

NDDS has many advantages in cancer treatment, including the effectiveness and duration of specific drug activity, and it also increased patient compliance compared to the drug, reducing the effect. Different types of novel formulations have been reported from polymeric nanoparticles, nanocapsules, liposomes, phytosomes,nanoemulsions microspheres and hydrogels using bioactive and plant extracts. The new formulations were reported to have significant advantages over conventional anticancer agent including solubility bioavailability, protection against toxicity, increased pharmacological activity greater stability, better distribution into tissue macrophages, sustained transport, and protection from physicochemical degradation of the drug.

Protein Kinase - The protein kinase enzyme is one of the most important drug targets in the 21st century, as the regulation of protein kinase activity is disrupted in several diseases, including cancer. Protein kinases play a crucial role in intracellular transduction due to their ability to phosphorylate a large number of proteins. In recent years, various protein kinase inhibitors have been identified and used effectively in the clinical field. In 2020, the FDA approved the following drugs for the treatment of listed diseases: gastrointestinal stromal tumours, capmatinib (non-small cell lung cancer), pemigatinib (cholangiocarcinoma), pralcetinib and

selpercatinib (non-small cell lung cancer), medullary thyroid cancer and differentiated thyroid cancer), selumetinib (neurofibromatosis type I) and tucatinib (neurofibromatosis type I) (HER2-Positive breast cancer).

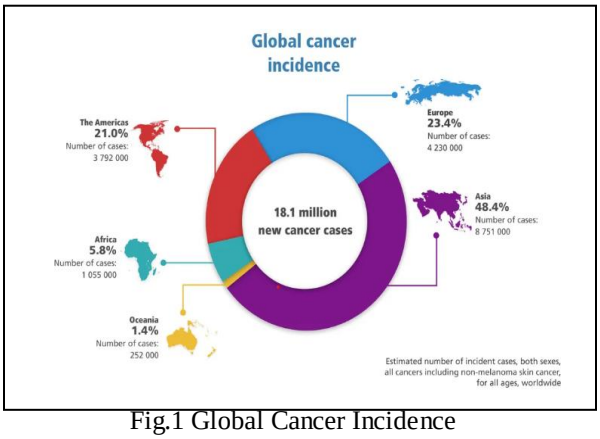

Fig.1 Global Cancer Incidence

Protein kinases belong to a large family of kinases and are responsible for the phosphorylation mechanism. They are activated by phosphorylation, which in turn activates a series of events that lead to phosphorylation of different amino acids . The kinase is activated or deactivated in different ways:

By cis-phosphorylation/autophosphorylation through the kinase itself, by binding to activating or inhibitory proteins, or by controlling their position in the cell in relation to the substrate. The catalyst protein kinase domain has 2 subdomains, N- and C-terminus. Both are connected by a peptide backbone, which forms a front pocket (catalytic residues) and a back pocket of the active site. Access to the rear pocket is regulated by a conserved lysine residue and a "gatekeeper" residue. The catalytic domain is not available as active because the N- and C-terminal subdomain helices rotate inward. Activation of the catalytic domain occurs through phosphorylation of the activation loop or an allosteric mechanism In addition, kinases also have non-catalytic domains that allow them to bind to substrates and recruit other signaling proteins Kinase activity can modify up to 30% of all human proteins, and kinases can regulate most cellular ones. pathways, especially those involved in signal transduction

Role of protein kinase in cancer –

Phosphorylation can lead to conformational changes that can modulate biochemical functions and configure tightly regulated biological networks . Deregulated kinase signaling has been associated with cancer markers . Oncogenic transformation of kinases has been associated with amplification, genomic rearrangements, gain-of-function mutations, deletions of kinase genes or dysregulation of downstream kinase signaling . Such deregulation can lead to altered kinase expression and function and tumorigenesis and survival. An example of such deregulation is the BRAF proto-oncogene gene mutant encoding the serine/threonine protein kinase B-Raf, which occurs in 40-50% of melanoma cases . Importantly, V600E is a dominant BRAF mutation that renders the mitogen-activated protein kinase (MAPK) pathway constitutively active, leading to increased cell proliferation . Another well-known oncogene is the epidermal growth factor receptor (EGFR), which belongs to the ErbB family of tyrosine kinases. Activating EGFR mutations and overexpression of EGFR proteins lead to signaling disturbances and give tumor cells a growth advantage, stimulating proliferation, survival and metastasis..

Cell signaling pathway -. Protein phosphorylation is one of the most common and important post-translational modifications (PTMs) This reversible mechanism occurs through protein kinases and consists of the addition of a phosphate group (PO4) to the polar group R of various amino acids. Consequently, this addition modifies the protein from hydrophobic apolar to hydrophilic polar, allowing the protein to change conformation when interacting with other molecules. A phosphorylated amino acid can bind molecules able to interact with other proteins and consequently assemble and detach proteic complexes The interactive capacity of the phosphate group is mainly due to its components. One of its main elements is phosphorus. It has five outer electrons able to form a maximum of five covalent bonds, has three pKas, high water solubility and it can form, for its versatility, mono, di and trialkyl and aryl esters with hydroxyl groups, but also acid anhydrides In particular, many cellular phosphate esters are phosphoproteins that form, via a catalytic enzyme and adenosine triphosphate (ATP), a phosphate anhydride, acting as a donor of a phosphate group.A good energy balance also favours phosphorylation. Indeed, there is a constant balance between phosphorylation and DE phosphorylation events mediated by kinases, phosphatases, ATP and/or ADP (protein + ATP ⇄ phosphoprotein + ADP)

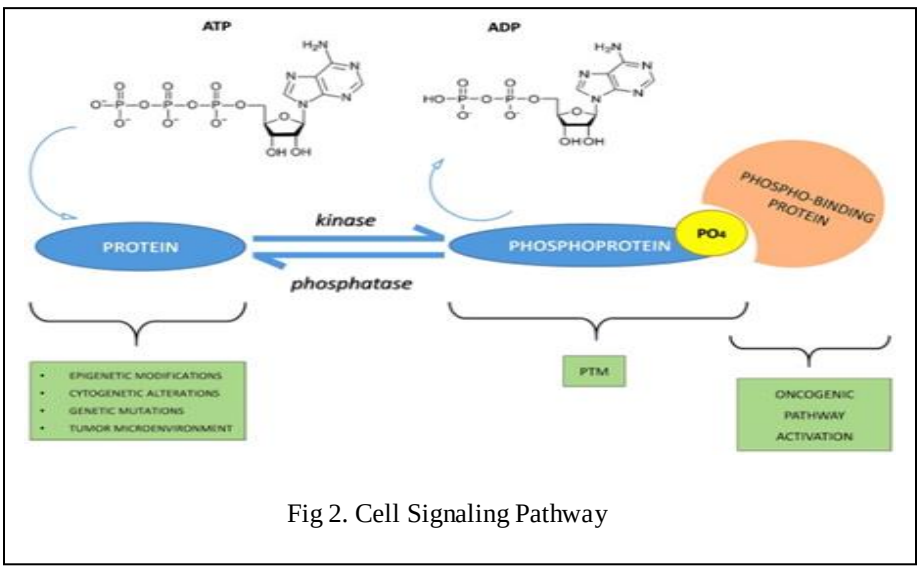

Fig 2. Cell Signaling Pathway

One of the most important functions of protein kinase in cell signaling is phosphorylation. Phosphorylation is a very important type of modification. After the molecule is phosphorylated, the kinase transfers the γ-phosphate of ATP to it. Phosphorylation of a protein can either activate or inhibit it. The AP-1 (Fos/Jun) transcription factor cJun contains phosphorylation sites at the N terminus and near the downstream DNA binding site. N-terminal phosphorylation (by MAPK family members) is involved in the activation of cJun, while phosphorylation near the DNA binding site (by GSK-3) silences cJun [70Phosphorylation of tyrosine residues can also create highly selective docking sites for SH2 or other PY-binding domain-containing proteins. The presence of protein phosphatases allows switching between the active and inactive states of proteins and their complexes: they dephosphorylate their targets by removing phosphate modifications.

1. The CaMK group of protein kinases in cell signaling

CaMK group serine/threonine protein kinases also usually control basic amino acids. Regulation through secondary communication pathways is also common for this group. The CaMK group includes the Ca2+/calmodulin-dependent kinase (CaMK) and SNF1/AMPK families.

2.The CMGC Group of Protein Kinases in Cell Signalling

The serine/threonine kinases of the CMGC group are not regulated by second messengers but function further downstream in protein kinase cascades. These kinases usually have regulatory phosphorylation sites in the activation segment. The CMGC group includes the CDK (cyclin-dependent kinase) family, the MAPK/ERK family, the GSK-3 family, and the Clk (Cdc-like kinase) family.

3.Traditional group of protein tyrosine kinases in cell signaling

The traditional group of protein tyrosine kinases (PTKs) differs from all other groups in that members exclusively phosphorylate tyrosine residues. PTKs are often involved in growth and differentiation signaling in metazoans. The main differences between serine/threonine and conventional tyrosine kinases are in the catalytic loop and the activation segment. A sequence corresponding to the HRDLKxxN motif in the catalytic loop (subdomain VIb) shows serine/threonine specificity; HRDLRAAN and HRDLAARN are consequences indicating conventional non-receptor PTKs andRTKs,Respectively. The activation segment has a conserved threonine in serine/threonine kinases; In PTKs, the corresponding residue is proline. This may create a more open site for a larger tyrosine substrate residue.

4. Group of "Other" Protein Kinases in Cell Signaling

Protein kinases outside the four main groups are grouped into a group of "other" kinases, including the MEK/Ste7p family, the MEKK/Ste11p family, the PAK/Ste20p family, the Raf family, the activin/TGF-β receptor family, the flowering plant receptor kinase family, casein kinase I family and LIM kinases.

Overview of the human kinome and its diversity

The kinome, encoded by approximately 2% of the human genome, is one of the largest superfamilies' of homologous proteins, consisting of 538 kinases, the human kinome includes lipid and protein kinase, protein kinase, 478. includes eukaryotic proteins. protein kinase (ePK) the remaining 40 kinases have no sequence similarity to the ePK domain, may have kinase activity. Therefore, they are called atypical protein kinases. (aPKs).Kinases have been found in most organelles, and studying their intracellular localization at the proteome level facilitated kinome mapping. Imaging-based approaches used labelled antibodies to visualize proteins. For example, the Human Protein Atlas (HPA) Cell Atlas project has mapped more than 12,000 proteins to 13 major organelles using antibodies against endogenous proteins. However, reliability was limited by the specificity of the antibody in such a single antibody, single protein. is approaching.

Table.1 Various types of kinases & Their descriptions

Kinase	Description
AGC	Containing PKA, PKG, PKC families
CAMK	Calcium/calmodulin-dependent protein kinase
CK1	Casein kinase 1
CMGC	Containing CDK, MAPK, GSK3, CLK families
STE	Homologs of yeast Sterile 7, Sterile 11, Sterile 20 kinases
TK	Tyrosine kinase
TKL	Tyrosine kinase-like

Classification of protein kinases -.

Classification - Protein kinases are classified into five main groups based on the amino acid residues they phosphorylate, including serine/threonine protein kinases (ST-PKs), tyrosine protein kinases (TKS), histidine-specific kinases. , bispecific protein kinases, and aspartic/glutamic acid-specific protein kinases.

1.Serine/threonine protein kinase - Serine/threonine protein kinase is a large family of protein kinases, which mainly include the following kinases: cyclin-dependent kinase, mitogen-activated protein kinase, protein kinase D, nattokinase, DNA. -dependent protein kinase, and aurora protein kinase, and pancreatic kininogenase.

A.Cyclin-dependent kinase: Cyclin-dependent kinases (CDK) are serine/threonine kinases. A sub unit of CDKs must bind to the corresponding cyclin to be activated. Activated CDKs have protein kinase activity that phosphorylates various substrate proteins and thus initiates or regulates the cell cycle. The substrate activated by CDKs mainly includes retinal glioma protein, tumor suppressor gene p107, p103, etc., which play an important role in promoting cell cycle phase transition, initiating DNA synthesis, promoting cell division and promoting cell cycle function. CDKs are also involved in the regulation of neuronal transcription, mRNA processing and differentiation of neural cells.

This phosphorylation typically occurs on a specific threonine residue, leading to a conformational change in the CDK that enhances its kinase activity. The activation forms a cyclin-CDK complex which phosphorylates specific regulatory proteins that are required to initiate steps in the cell-cycle.

B. Mitogen-activated protein kinase: Mitogen-activated protein kinases (MAPKs) are a class of cellular serine/threonine protein kinases that are essential components in theregulation of embryogenesis, cell differentiation, cell proliferation and cell death. MAPKS is involved in controlling cellular responses to various stimuli, such as mitogens, osmotic stress, heat shock and pro-inflammatory cytokines.Mitogen-activated protein kinases are catalytically inactive in their native form, requiring activation by

phosphorylation. MAP kinase is regulated by a phosphorylation cascade. It is regulated by a three-level cascade consisting of MAP kinase, MAPK kinase and MAPKKkinase. Each MAPK kinase, however, can be activated by more than one MAPKK kinase, increasing the complexity and diversity of MAPK signalling.

C. Protein kinase D: It belongs to a new class of serine/threonine protein kinase activated by protein kinase C (PKC). PKD is involved in the regulation of cellular functions such as Golgi cell reverse membrane transport,cell growth, proliferation,migration,differentiation and apoptosis.

PKD and cardiovascular: PKD protects the heart muscle and reduces damage to myocardial cells from calcium overload. PKD increases myocardial contractility,PKD and neurons: PKD affects transferrin receptor (TFR) and low-density receptor-related protein (LRP) transport in hippocampal neurons.PKD and immune regulation: PKD is also involved in regulating PKD and tumor cells: PKD can promote tumor invasion and metastasis by regulating matrix metalloproteinase (MMP) expression.

2. Tyrosine kinases

Tyrosine kinases are classified as non-receptor tyrosine protein kinases (NRTKs), receptor tyrosine kinases (RTKs), and nuclear protein tyrosine kinases.

•Non -receptor tyrosine protein kinases (NRTKs): essential domains. -receptor tyrosine protein kinases are mainly SHI, SH2, SH3, PH, PTB, etc., which play important roles in kinase catalytic reaction, enzyme localization, activity regulation and interaction with other molecules.

Non-receptor tyrosine protein kinases. are divided into 11 families with at least 30 members. They mediate the signaling of various growth factor receptors, cytokine receptors, lymphocyte antigen receptors and adhesion molecule integrins.

Non-receptor tyrosine protein kinase, which mainly includes:

1. SRC kinase family: a product of the protooncogene c-Src, involved in antigen receptors, cytokine receptors and integrin-mediated transmembrane signaling.

2.JAK kinase family (Janus kinase): including JAK1, JAK2, JAK3 and TYK2. They mainly mediate transmembrane signal transduction of cytokine receptors.

3.Sky/ZAP-70 family: including Sky and zeta chain-associated protein-70. It mediates signal transduction of lymphocyte antigen receptors and certain cytokine receptors, and is important in lymphocyte differentiation, development and activation.

In addition, Receptor tyrosine protein kinase also includes CSK family, Tec family and adhesion plaque kinase family, etc. We conclude the non-receptor tyrosine protein kinase

•Nuclear tyrosine protein kinase-

This involves transcriptional processes and cell cycle regulation.

3. Histidine-specific protein kinases.

Histidine protein kinase is a kinase that phosphorylates the histidine Substrate protein. Mainly includes:

Bicomponent histidine protein kinase, it can regulate response to environmental stimuli.

Bicomponent mammalian histidine protein kinase: branched chain α-ketoacid dehydrogenase kinase (BCKDHK) and pyruvate dehydrogenase kinase (PDHK).

4. Bispecific protein kinases

Bispecific protein kinases have bispecific kinase activity and can be for both serine/threonine and tyrosine.

A specific example of a different type of cancer-related kinase -Savolitinib

Savolitinib - Savolitinib is a very specific inhibitor of the MET tyrosine kinase. Both pre-clinical studies and clinical trials have shown its potential in the treatment of various cancers such as non-small cell lung cancer (NSCLC) and breast, head and neck, colon, stomach, pancreatic and other gastrointestinal cancers. It can be used as a stand-alone therapy in NSCLC patients with MET mutations and in combination. with EGFR inhibitors for those who have developed resistance. This In addition, evolution has been shown to be effective in the treatment of gastric cancer and may be effective in combination therapy. In addition, it has been shown to be effective in the treatment of kidney cancer and other gastrointestinal cancers.

Savolitinib is an orally bioavailable c-Met receptor tyrosine kinase inhibitor with potential antitumor activity. Savolitinib selectively binds to c-Met and inhibits its activation in an ATP-competitive manner and disrupts c-Met signaling pathways. This can lead to inhibition of cell growth in tumors that overexpress the c-Met protein. C-Met encodes hepatocyte growth factor receptor tyrosine kinase and plays an important role in tumor cell proliferation, survival, invasion and metastasis, and tumor angiogenesis; this protein is overexpressed or mutated in several cancers.

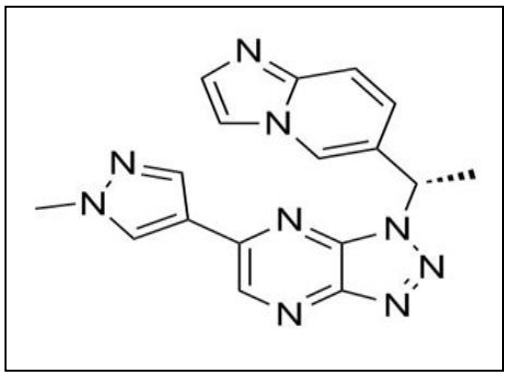

Fig 3. Chemical Structure of Savolitinib

Activity of Savolitinib -

Savolitinib is rapidly absorbed. The absolute oral bioavailability was 69%, medium.

The maximum observed concentration was 3.5 hours and the mean terminal half-life was 6.1. h) 56% was found in urine and 38% in feces. Approximately 3% of the administered dose was excreted in the urine as unmetabolized savolitinib. Savolitinib has moderate distribution, low to moderate clearance, and low accumulation.

Drug interaction

. A drug interaction was reported in which co-administration of rifampicin significantly reduced savolitinib exposure compared to savolitinib alone.

Safety profile - Savolitinib 600 mg showed a safety profile and promising antitumor activity in advanced EGFRm and MET amplified NSSCLC patients. received prior EGFR-TKI therapy.

Small molecule kinase inhibitors-

Small molecule kinase inhibitors (SMKIs) are drugs designed to inhibit the activity of enzymes called protein kinases. Protein kinases are like molecular switches inside cells that control many cellular processes, including cell growth, division, and survival. By inhibiting these enzymes, SMKIs can disrupt these processes and have therapeutic effects in various diseases.

.Small molecule kinase inhibitors have emerged as a promising class of drugs for the treatment of breast cancer due to their specific targeting of breast cancer growth and progression. targeting the kinase.Many type I kinase inhibitors are FDA-approved for the treatment of breast cancer.treatment. bosutinib, crizotinib, dasatinib, erlotinib, gefitinib, lapatinib, pazopanib, ruxolitinib, sunitinib, and vemurafenib.

Advantage - Small molecule inhibitors are very effective as antimicrobial enzymes that carry out biochemical enzyme reactions. for example, in building and maintaining cells.

Limitations -

Limited efficacy: a. The efficacy of small molecule kinase inhibitors may be affected by mutations or other genetic changes affecting the target kinase pathway and may not be effective in all . patients.

b. Despite significant progress, small-molecule inhibitors in cancer therapy face many obstacles, such as low response rates, short response time, toxicity, Small molecule kinase inhibitors and their targets in T cells: T cells also have many signaling molecules and pathways that target small molecule kinase inhibitors. Therefore, these inhibitors have the potential to mediate downstream effects such as cell proliferation and effector functions (cytokine production, cell lysis). The T-cell receptor (TCR)/peptide/MHC interface and some of the signaling pathways involved in TCR and other T-cell surface receptors such as CD25 (IL-2 receptor) and CD28 (costimulatory receptor) are described here.

ERK: extracellular signaling regulated kinase; TCR: T cell receptor.

How SMKIs work:

SMKIs bind to a specific site on a protein kinase, often the ATP-binding pocket. ATP (adenosine triphosphate) is a molecule that cells use as energy. When an ATP molecule binds to a kinase, it activates the enzyme and allows it to transfer a phosphate group (PO4) to another protein. This phosphorylation event can turn on or off the activity of the target protein.

By competing for the ATP binding site, SMKIs inhibit the activation of the kinase, thus preventing the phosphorylation of its target proteins. This can disrupt cell signaling pathways that are important for the development of the disease.

Examples of SMKIs approved by the FDA for the treatment of cancer include:

i)Imatinib (Gleevec) for chronic myelogenous leukemia (CML) and gastrointestinal stromal tumors (GIST)

ii)Erlotinib (Tarceva) for non-small cell lung cancer (NSCLC)

iii)Gefitinib (Iressa) For NSCLC.

Challenges for drug resistance and tumor heterogeneity-

Drug resistance in cancer-Drug resistance is a major obstacle in cancer treatment. This essentially renders the drug ineffective, allowing the cancer cells to survive and continue to grow. Here's a breakdown of the challenges posed by drug resistance:

Different mechanisms: Cancer cells can develop resistanceanceance through a variety of mechanisms, including:

i)Altered drug targets: Mutations in drug targets can prevent them from binding or working effectively.

ii)Drug Efflux Pumps: These pumps work like chemotherapy drugs, pushing chemotherapy drugs out of cells before they take effect.

ii)Better DNA Repair: Cancer cells can repair damage from chemotherapy, rendering it useless.

Decreased Cell Death: Some cancers . develop ways to prevent drug-induced cell death (apoptosis).

iv)Tumor heterogeneity: Tumors are not uniform. They contain a mixture of cells with different mutations. This diversity allows some cells to be resistant to treatment from the start, and resistant cells can multiply after exposure to the drug.

iv)Evolution Tactics: Cancer cells are constantly evolving. As new treatments are introducing resistance mechanisms arise. It's a constant game of adaptation for researchers and cancer patients.

These challenges complicate the development of long-term cancer treatments and require continued research to develop new strategies to overcome resistance.

Tumor heterogeneity-

Tumor heterogeneity, the variability within an individual tumor, represents several keys to cancer treatment plans. Here are some of its main challenges:

i.Precise diagnosis and biomarker detection: Tumor heterogeneity can make it difficult to get an accurate picture of cancer. A biopsy may only cover a small portion that may be missing important mutations or features. This can lead to inaccurate diagnoses and prevent the identification of effective biomarkers for targeted therapy.

ii.Treatment selection and resistance: Because different tumor subpopulations may have different genetic makeup, they may respond differently to therapy. A treatment that targets one mutation may be ineffective against another, allowing resistant subclones to survive and potentially take over. This heterogeneity is a major reason why tumors can develop resistance to treatment.

iii.Standardization of treatment: Developing a standardized treatment protocol is diff icult when treating such diverse tumors. A "one-size-fits-all approach" may not be effective, and tailoring treatment plans to individual patients based on their tumor structure is imperative.
iv.Drug development: Designing effective therapies is complicated by heterogeneity. Drugs must be broad enough to target multiple tumor subclones or be adaptable to target evolving mutations.
v.Despite these challenges, researchers are exploring ways to address tumor heterogeneity. This includes:
viMulti-site sampling: taking biopsies from different areas of the tumor to get a more complete picture.
vii.Advanced sequencing methods: single-cell sequencing allows analysis of individual cancer cells to understand the different mutations present.
viii.Combination therapies: combining drugs, targeting different pathways or mutations in a tumor to increase efficacy to improve and reduce resistance.
ix.Personalized medicine: tailoring treatment plans based on the specific genetic makeup of a patient's tumor.
can overcoming these challenges with strength. due to the heterogeneity oftumors, researchers hope to develop more effective and long-lasting treatments for cancer patients.

Future directions and perspective

Although only a small fraction of the kinome is currently targeted, the discovery of kinase inhibitors has progressed dramatically over the past decade. Clinical evaluation of kinase inhibitors has shown that therapeutic responses vary widely between individual patients and patient populations and appear to depend on many different factors. Many new candidate molecules have entered clinical trials and many others are still in preclinical stages. Most current kinase inhibitor discoveries have been developed through rational drug design rather than random screening and analysis of structure–activity relationships. An important strategy for future development is to understand the basis of unexpected toxicity associated with kinase inhibitors. Improving the documentation of kinase inhibitor toxicity would provide a valuable database for understanding whether there are specific kinases that should be avoided or specific substructures that lead to problematic metabolites. This strategy will help develop kinases with better selectivity that will benefit a broad patient population. In addition, there is a critical need for better ways to monitor target kinase inhibition in humans using minimally invasive techniques. This may include tracking cancer biomarkers that can serve as benchmarks for the clinical development of kinase inhibitors. The development of such methods will help find and eradicate tumour's using targeted kinase inhibition with minimal toxicity. There is also an urgent need todevelop more non-ATP competitive kinase inhibitors, as the current pool of kinase inhibitors is limited to ABL, IKK, AKT, CHK1, MEK, SRC, IGF1R inhibitor. In addition, there is a need to develop sophisticated modelling of chemotherapy resistance in response to kinase inhibitors. This helps to overcome kinase resistance and allows the systemic use of combinations of kinase inhibitors. In addition, new preclinical models are needed to identify the best kinase inhibitor cocktails with natural bio actives.
Advanced high-throughput cell-based screening using well-defined phosphorylation lists should be implemented. However, screening and developing natural kinase inhibitors using only cell counts can prove difficult. It is also important to understand that kinase inhibitors are not only important in cancer therapy, but also help us better understand the physiological functions of kinases. In the field of oncology, kinase inhibitors have been shown to be well tolerated compared to conventional cytotoxic chemotherapy. The future of kinase-targeted cancer therapy appears promising, and implementation of these strategies will help achieve therapeutic advances and overcome treatment barriers.

Conclusion-

It is clear that PKC isoforms are involved in cancer progression and are important targets for cancer therapy. The biological functions of PKC isoforms probably differ in different tumor types. This also explains why many attempts to target PKC isoforms in cancer have met with very limited success.Most FDA-approved kinase inhibitors target the ATP-binding site of kinase enzymes and have therapeutic indications against tumorigenesis. This class of therapeutic agents represents a transition from conventional chemotherapy to targeted cancer therapy. Kinase inhibitors have overcome a major shortcoming of traditional Cancer treatment by effectively distinguishing treatment by effectively distinguishing normal, non-malignant cell from rapidly multiplying cancer cells. This results in fewer side effects and low toxicity in the cancer patient population. Kinase inhibitors are also often useful in combination with cytotoxic chemotherapy or radiation therapy. Although still challenging, further advances in this technology are expected to facilitate the identification of kinase drug candidates with improved therapeutic efficacy, overcome therapeutic barriers caused by drug resistance and ultimately improve clinical cancer outcomes for patients.

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