Chapter

Introductory Chapter: Protein Kinases as Promising Targets for Drug Design against Cancer

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1. Introduction

Cancer is one of the most dreadful and highly prevailing life-threatening ailments of the modern age. Despite a great advancement in the health sector, still it is the leading cause of mortality around the globe [1, 2]. The continuous research is in progress for several years to design therapeutic agents against cancer with greater efficacy, specificity, and least toxicity. For the past two decades, the protein kinase family has been greatly focused by the researchers for drug development against cancer. There are about 538 protein kinase enzymes that are encoded by the human genome, which function mainly by transferring a γ-phosphate group from the ATP site toward amino acid residues such as serine, threonine, or tyrosine residues [3–5]. It is evident that several members of this protein kinase family have tendencies to initiate and develop human cancers [6, 7]. The recently developed small molecules as potential kinase inhibitors in the therapy of a variety of cancers have witnessed the significance of kinases as a target against cancers. Moreover, these are in second place as a target for drugs after the G-protein-coupled receptors [8]. Protein kinases are associated with the promotion of cell proliferation, migration, and survival and, when they are dysregulated/overexpressed, lead to oncogenesis [9, 10]. During the past decades, it has been observed that human malignancies are largely associated with modulation or dysfunction of protein and lipid kinases due to the deactivation of phosphatases resulting from chromosomal abnormalities or mutations [11, 12]. It is worth notable that the anti-inflammatory kinases such as EGFR, VEGFR, BCR-ABL, ALK, KIT, HER2, and several others are involved in the development of solid cancers including chronic lymphoid leukemia, lymphoblastic leukemia, mantle cell lymphoma, myelogenous lymphoma, and several other types of cancers [13]. These kinases show a pro-tumor effect associated with loss of normal kinase functioning followed by mutations and associations with high-regulatory T cell pathogens [14]. These pathogens ultimately activate the anti-inflammatory kinases and initiate the development of solid cancers. The role of some kinases in the development of cancers has been depicted in Figure 1.

Kinase amplifications are able to play diagnostic, prognostic, therapeutic as well as biomarker roles in cancer [15]. The amplifications of EGFR have been well seen in a variety of cancers including non-small cell lung cancer, colorectal cancer, bladder cancer, pancreatic, and breast cancer, whereas ERBB2 amplifications are associated with esophageal, gastric, breast, and ovarian cancers [16–18]. Overexpression of EGFR, ERBB2, EPHA2, and AKT2 are the best examples of biomarkers for cancers [19, 20].
2. Progress in the development of protein kinase inhibitors against cancer

In the past two decades, there has been a remarkable progress made in the drug development process involving protein kinases as a target. The first FDA approved drug imatinib was launched in 2001 against chronic myeloid leukemia which inhibits Abelson (ABL) tyrosine kinase \[21\]. It was proved to be a blockbuster drug with polypharmacological effects. From 2001 to 2021, in a span of 20 years, there has been an extraordinary progress made with the discovery of more potent and specific small-molecule kinase inhibitors and about 70 new drugs have got approval in this time span \[22\]. These drugs have left a promising positive impact to improve the drug design strategies and therapy to treat the cancers and conditions associated with it. Table 1 comprises the details of kinase inhibitor drugs approved by the FDA from 2015 to 2021 \[23–58\].

The modern strategies adopted for the development of selective kinase inhibitors include synthesis along with structure-based design approaches facilitated by molecular docking, crystallographic studies, and NMR spectroscopy \[59\]. It is surprising that alone USA has filed more than 10 thousand patent applications for kinase inhibitors since 2001. Beyond the discovery of small-molecule kinase inhibitors, kinase-targeted antibodies have also been postulated against different cancers such as cetuximab (colorectal, head, and neck cancer), trastuzumab (breast cancer) \[60\]. Various small-molecule kinase inhibitors have different inhibitory modes and on the basis of these modes, these inhibitors have been divided into five categories (Figure 2). Type I inhibitors contain a heterocyclic moiety in their structure to occupy purine binding pocket and serves as a template for side chains to occupy the hydrophobic region. These inhibitors are basically ATP-binding site competitors and mimic the purine ring of ATP. These bind to the active conformational side and cause alteration of structural conformation \[61\]. Type II inhibitors target the inactive conformation and occupy the catalytic region of the unphosphorylated inactive conformation. These kinases explore the new binding patterns in the hydrophobic pocket associated with conformational changes of phenylalanine residue of the Asp-Phe-Gly (DFG) system \[62\]. Type III inhibitors are regarded as allosteric inhibitors and exhibit their action via binding to the outer catalytic ATP-binding site and alter kinase activity in an allosteric
| S. No. | Drug     | Brand name | Year of approval | Inhibitory target         | Indication                                           | References |
|-------|-----------|------------|------------------|---------------------------|-----------------------------------------------------|------------|
| 1     | Palbociclib | Ibrance    | 2015             | CDK4/6 inhibitor          | Advanced metastatic breast cancer                   | [23]       |
| 2     | Lenvatinib | Lenvima    | 2015             | VEGFR1/2/3 inhibitor      | Progressive/ differentiated thyroid cancer           | [24]       |
| 3     | Cobimetinib | Cotellic   | 2015             | MEK inhibitor             | Melanoma                                            | [25]       |
| 4     | Osimertinib | Tagrisso   | 2015             | EGFR inhibitor            | Non-small cell lung carcinomas with specific mutations| [26]       |
| 5     | Necitumumab | Portrazza  | 2015             | EGFR antibody             | Advanced (metastatic) squamous non-small cell lung cancer | [27]       |
| 6     | Alectinib  | Alecensa   | 2015             | ALK inhibitor             | Non-small cell lung cancer                          | [28]       |
| 7     | Olaratumab | Lartruvo   | 2016             | PDGFRA inhibitor          | Soft tissue sarcoma                                  | [29]       |
| 8     | Ribociclib | Kisqali    | 2016             | CDK4/6 inhibitor          | Advanced breast cancer                               | [30]       |
| 9     | Brigatinib | Alunbrig   | 2017             | ALK and EGFR inhibitor    | Non-small cell lung cancer                          | [31]       |
| 10    | Copanlisib | Aliqopa    | 2017             | PI3K inhibitor            | Relapsed follicular lymphoma                         | [32]       |
| 11    | Abemaciclib | Verzenio   | 2017             | CDK4/6 inhibitors         | Advanced metastatic breast cancer                   | [33]       |
| 12    | Acalabrutinib | Calquence | 2017             | BTK inhibitor             | Mantle cell lymphoma                                 | [34]       |
| 13    | Binimetinib | Mektovi    | 2018             | MEK inhibitor             | Unresectable or metastatic melanoma                 | [35]       |
| 14    | Encorafenib | Braftovi   | 2018             | MEK inhibitor             | Unresectable or metastatic melanoma                 | [36]       |
| 15    | Duvelisib  | Copiktra   | 2018             | PI3K inhibitor            | Refractory chronic lymphocytic leukemia, small lymphocytic lymphoma, and follicular lymphoma | [37]       |
| 16    | Dacomitinib | Vizimpro   | 2018             | EGFR inhibitor            | Metastatic non-small cell lung cancer               | [38]       |
| 17    | Lorlatinib | Lorbrena   | 2018             | ALK and ROS1 inhibitor    | Metastatic non-small cell lung cancer               | [39]       |
| 18    | Gilteritinib | Xospata   | 2018             | AXL inhibitor             | Relapsed or refractory acute myeloid leukemia       | [40]       |
| 19    | Erdafitinib | Balversa   | 2019             | FGFR inhibitor            | Locally advanced or metastatic bladder cancer       | [41]       |
| 20    | Alpelisib  | Piqray     | 2019             | PI3K inhibitor            | Breast cancer                                       | [42]       |
| 21    | Pexidartinib | Turalio   | 2019             | inhibitor of CSF1, KIT, and FLT3 | Symptomatic tenosynovial giant cell tumor             | [43]       |
Type IV kinase inhibitors are regarded as substrate-directed inhibitors and undergo reversible binding outside the ATP pocket. These are non-competitive inhibitors and do not compete with ATP [63]. Type V inhibitors are covalent inhibitors and bind through an irreversible covalent bond to catalytic nucleophilic cysteine active site of the enzyme.

### Table 1.
**FDA-approved kinase inhibitors against various cancers during 2015–2021.**

| S. No. | Drug               | Brand name | Year of approval | Inhibitory target | Indication                                           | References |
|--------|--------------------|------------|------------------|-------------------|-----------------------------------------------------|------------|
| 22.    | Entrectinib        | Rozlytrek  | 2019             | inhibitor of ALK, ROSI, TKI, and TRKA/B/C | Metastatic non-small cell lung cancer | [44]       |
| 23.    | Zanubrutinib       | Brukinsa   | 2019             | BTK inhibitor     | Mantle cell lymphoma                                | [45]       |
| 24.    | Avapritinib        | Ayvakit    | 2020             | PDGFRA receptor kinase inhibitor | Metastatic gastrointestinal stromal tumors | [46]       |
| 25.    | Selumetinib        | Koselugo   | 2020             | BRAF kinase inhibitor | Neurofibromatosis type I                             | [47]       |
| 26.    | Tucatinib          | Tukyssa    | 2020             | EBBR2 inhibitor   | Metastatic HER2-positive breast cancer              | [48]       |
| 27.    | Pemigatinib        | Pemazyre   | 2020             | FGFR2 inhibitor   | Advanced/metastatic or surgically unresectable cholangiocarcinoma | [49]       |
| 28.    | Capmatinib         | Tabrecta   | 2020             | MET kinase inhibitor | Metastatic non-small cell lung cancer             | [50]       |
| 29.    | Selpercatinib      | Retevmo    | 2020             | RET receptor kinase | Non-small cell lung cancer, metastatic medullary thyroid cancer, or advanced or metastatic thyroid cancer | [51]       |
| 30.    | Ripretinib         | Qinlock    | 2020             | PDGFRA and KIT receptor kinase inhibitor | Gist                                               | [52]       |
| 31.    | Pralsetinib        | Gavreto    | 2020             | RET receptor kinase inhibitor | Thyroid cancer, non-small cell lung cancer | [53]       |
| 32.    | Margetuximab       | Margenza   | 2020             | HER2 inhibitor     | HER2-positive breast cancer                          | [54]       |
| 33.    | Trilaciclib        | Cosela     | 2021             | CDK4/6 inhibitor   | Extensive-stage small cell lung cancer              | [55]       |
| 34.    | Infigratinib       | Truseltiq  | 2021             | FGFR2 inhibitor    | Cholangiocarcinomas with FGFR2 fusion proteins      | [56]       |
| 35.    | Tepotinib          | Tepmetco   | 2021             | Met Kinase         | Met mutation-positive non-small cell lung carcinoma | [57]       |
| 36.    | Tivozanib          | Fotvida    | 2021             | VEGFR2 inhibitor   | Renal cell carcinoma                                | [58]       |
From a clinical point of view, it has been observed that kinase target anticancer therapies have more success rate than the other cancer therapies. But it is also evident in the past few years EGFR/VEGF-targeting molecules have given unsatisfactory results [64, 65]. Instead, success stories have been seen with molecules targeting kinase B, phosphatidylinositol kinase delta and gamma, kinase I, tyrosine kinase, nerve growth receptors Wee 1-like kinases in Phase 1 clinical trials. The latest explored targets Aurora kinases have led to the development of two inhibitors palbociclib and ribociclib which have passed phase III clinical trials [66]. The modern developments on kinases are following the precision therapy that has been based upon the genomic data. The detailed genetic studies on tumors and drivers involved in the generation of tumors have resulted in tremendous advantages for patients who need effective therapy.

3. Investigations on kinase inhibitory potentials of natural products

The continuous research is in progress for several years to design synthetic and natural chemotherapeutic agents against cancer with selective cytotoxic efficacy and minimum toxicity [67–70]. The contribution of molecules from natural sources in kinase-mediated anticancer research cannot be ignored. The kinase modulating properties of natural molecules has brought a new paradigm in the screening of kinase inhibitors. Toward this direction, small molecules like polyphenols have revealed tremendous potentials to bind with kinases like tyrosine kinase followed by alteration of phosphorylation leading to modulation of multi-signaling mechanisms. The explored natural compounds in this direction are curcumins, resveratrol, quercetin, cyrystitin, myricetin, luteolin, apigenin, anthocyanin,
genistein, epigallocatechin gallate, fisetin, astaxanthin, and tetrahydrocurcumins and many more. Polyphenols such as resveratrol [71], quercetin [72], curcumin [73] and tea extracts [74] have revealed promising EGFR inhibition [75]. Curcumin and chrysin have receptor RON blocker activity in tumor cells [76, 77]. Natural products have also shown Abl, JAK-2, c-Met, c-SRC, and serine kinase inhibitory potentials [78–80]. Resveratrol also has modulatory effects on the expression of Akt in breast, uterine, skin, and prostate cancers [81, 82]. It binds to the ATP site competitively as well as reversibly. Myricetin has reported inhibition of cell proliferation by binding to Akt. Beyond these significant activities, several reports in the literature are available evidencing the inhibitory and modulatory effects of natural products on mTOR, CDK, Aurora kinases, B-raf kinases, PI3K [83–85], etc. Many natural molecules bind directly to the oncogenic kinases and alter the cell signaling involved in tumor progression by modifying the phosphorylation process. Several other classes of natural compounds are under investigation for their kinase-modulating activities.

4. Conclusions and future perspectives

The therapeutic implication of protein kinases against a variety of cancers is well known from past decades. Also, it is well established that deregulation, mutations, and overexpression of these kinases are important triggers for the development of cancers. Several kinase inhibitors are already reported who prevent cancer by modulating the protein kinases by following different mechanisms and several inhibitors are under investigation. Despite tremendous advancements in kinase drug development, still, a large number of kinases are unexplored. It is also worth notable that most of the available kinase inhibitors work through binding to ATP sites. A great challenge in clinical implication of kinase inhibitors is the development of drug resistance of cancer stem cells. It develops due to the loss of activity of some important kinases. Therefore, strategies to overcome this resistance are the requirement of the hour. In the therapeutics of cancer, the kinase inhibitors have been proven to be well tolerated as compared to the traditional therapies.

Abbreviations

ABL    Abelson murine leukemia viral oncogene
Ab1    Abelson murine leukemia
Akt    protein kinase B
ALK    anaplastic lymphoma kinase
BRAF   proto-oncogene
BTK    Bruton agammaglobulinemia tyrosine kinase
CDK    cyclin-dependent kinase
c-Met   c-MET proto-oncogene
c-SRC   proto-oncogene tyrosine-protein kinase
CTK    cytoplasmic tyrosine kinase
EGFR   epidermal growth factor receptor
ERBB2  V-Erb-B2 avian erythroblast leukemia viral oncogene homolog
FGFRs  fibroblast growth factor receptors
HER-2  human epidermal growth factor receptor-2
JAK2   Janus kinase 2
MAPK   mitogen-activated protein kinases
MEK    MEK kinase gene
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