Targeting CDKs with Other Chemotherapeutic Drugs: A Combinatorial Approach

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13.1 An Introduction to Cell Cycle

Cell division is an important aspect and fundamental process of various biological activities including tissue regeneration, homeostasis, pathological processes, various physiological activities, and tumorigenesis. The cell cycle is a succession of events by which a cell duplicates its genome and culminates with the formation of two daughter cells. It has two important phases, viz, interphase and M-phase (period of actual division). Interphase is the time during which cell prepares for division by experiencing cell growth and DNA replication. Interphase is divided into 3 phases—G1, S (synthesis phase), and G2 (Fig. 13.1). In the G1 phase the cell prepares for the DNA replication that is regulated by a "restriction point" in mammals. The cell can gain entrance into the cell cycle depending upon various extrinsic (such as growth factors) as well as intrinsic factors (like protein synthesis). Unavailability of any of these factors will lead to cell cycle arrest and entry into Go phase, a dormancy phase. Once the restriction point is passed, the cell is then committed to divide. Cell cycle regulation includes three "check-points"—G1/S, G2/M, and mitotic spindle checkpoints. Several studies have revealed that cyclin-dependent kinases (CDKs) are key drivers of eukaryotic cell cycle that promote the synthesis of DNA and chromosome segregation by phosphorylation of their substrate (Arellano and Moreno 1997, Swaffer et al. 2016). Forfeiture of control over cell cycle is a trademark of cancer. Progression from one phase to next phase of cell cycle requires cyclins and CDKs. Replenishing cell cycle control via CDK inhibition might open some windows for development of targeted cancer therapy.

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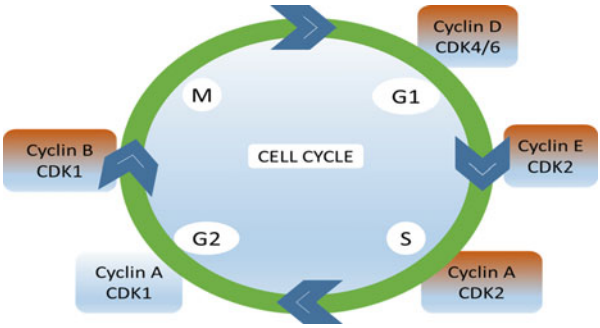


Fig. 13.1 Cyclin and their CDK partners in cell cycle

13.2 CDKs (Cyclin-Dependent Kinases)

CDKs are not just involved in the cell cycle but also have other important functions, such as insulin production, transcription, neuronal functions, and glycogen synthesis (Lim and Kaldis 2013). Until today, based on the homologous sequences in the human genome nearly 21 CDKs and 5 CDK-like genes have been recognized (Malumbres and Barbacid 2009). CDK1 is a critical β determinant of mitotic progression whereas CDK2 is more associated with DNA replication in higher eukaryotes. CDK4/6 promote entry into cell cycle especially G1-S transition in response to various growth signals (Morgan 1997, Mir et al. 2020). Besides cell cycle regulation other cyclin-dependent kinases (CDKs) also participate in cell cycle regulation including CDK7, CDK8, CDK9, and CDK11 (Sofi et al. 2022a, b). CDK7 phosphorylates RNA polymerase II to initiate transcription of genes. CDK8 is a component of the mediator complex which regulates enormous number of genes. CDK9 phosphorylates RNA pol. II and hence stimulates elongation of transcription. CDK11 mostly acts on the splicing machinery. Many evidences suggested that these transcription-associated CDKs can possibly act as probable therapeutic targets for cancer remedy (Qayoom et al. 2022, Sofi et al. 2022a, b). Additional type of CDKs called atypical CDKs are involved in various signaling pathways and post-mitotic functions. These include CDKs 5, 14, 15, 16, 17, and 18. CDK5 plays multiple post-mitotic functions (Mehraj et al. 2022a, b, c, d), while amalgam of CDK14 and Y cyclin is believed to play an important role in β-catenin signaling pathway (Davidson et al. 2009, Jiang et al. 2009). The cell cycle functions in a systematic and sequential manner that is attained by a careful sequence of phases and checkpoints that are regulated by a number of specific proteins that interact with specific cyclin-dependent kinases (CDKs) and maintain the progression of the cell cycle properly (Mehraj et al. n.d., Hanahan and Weinberg 2011). Anomalies in cyclin–CDK–Rb pathway are often associated with breast cancers. Therefore, targeting cancers by inhibiting CDKs will bring into control the cell cycle progression and prove beneficial in the development of targeted cancer therapy (Dickson 2014, Mehraj et al. 2022a, b, c, d). Further the CDKs are not degraded during the course of cell cycle unlike their regulatory counterparts, i.e. cyclins.

As CDKs are critical regulators of transcription, cell cycle, and other important biological functions, inhibitors against these CDKs have come into existence to treat multiple malformations associated with CDK dysfunctions. For over 20 years, many compounds have been developed against the abnormally activated CDKs and some are under clinical trials. Here we will discuss some of CDK inhibitors in synergism with other therapeutics.

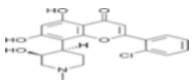
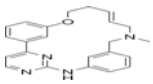
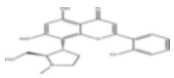
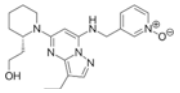
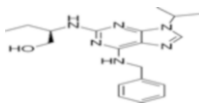
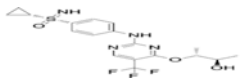
13.3 Pan-CDK Inhibitors

CDK inhibitors have been studied since the onset of 1990s, and pan-CDK inhibitors are the first generation of CDK inhibitors including Roscovitine and Flavopiridol, etc. The primary role of the pan-CDK inhibitors is to induce cell cycle arrest and hamper cell proliferation by obstructing CDKs activity. Because of their low specificity and toxicity most of the first-generation pan-CDK inhibitors failed in the clinical trials (Meijer et al. 1997, Mehraj et al. 2021a, b, c). Therefore, second-generation pan-CDK inhibitors such as RGB-286638, AT519, Dinaciclib, TG02, Roniciclib, P276-00, etc., were developed with improved selectivity and reduced cytotoxicity, and have shown good activity in pre-clinical trials with further verification needed. In addition, several pan-CDK inhibitors have gained entry into multiple phase trials and many others have shown promising anti-cancer activity in pre-clinical studies. To improve the efficacy of pan-CDK inhibitors, a number of studies have been performed on drug delivery, most importantly on combination therapy. Despite showing some significant efficacy pan-CDK inhibitors have shown some side effects and safety concerns. However, recent advancements in combination therapeutic approaches are giving positive results in lowering side effects and toxicity of pan-CDK inhibitors. Presently >40 pan-CDK inhibitors are rooming in various clinical stages of development (Mehraj et al. 2021a, b, c, Zhang et al. 2021). In Table 13.1, some pan-CDK inhibitors are represented having their respective targets, phases of clinical trials, and biomarkers of disease. Given below are some pan-CDK inhibitors.

13.3.1 Flavopiridol (Alvocidib)

Flavopiridol is a semisynthetic flavonoid. It is a first-generation pan-CDKI that has been studied on large scale and used in clinical trials. It quenches the activity of multiple CDKs, namely, CDK1, 2, 4, 6, 7, and 9 (Fig. 13.2) (Lin et al. 2010). It also targets positive transcription elongation factor P-TEb (Chao et al. 2000). Pre-clinical study sentenced that flavopiridol has anti-cancer activity in case of prostate cancer, thereby lowers 85% tumor size and improves survival by 30 days (Zeidner and Karp 2015). Despite pre-clinical research, flavopiridol has shown depreciation in efficacy throughout clinical trials of solid tumors and showed some side effects like cardiac dysfunction in AML patients and gastrointestinal toxicity in rodents. This limited the clinical trials of flavopiridol. Therefore, scientists are trying to use it with other drugs, especially paclitaxel, to refine its clinical efficacy (Zeidner and Karp 2015).

Table 13.1 Pan-CDK inhibitors

Name	Alternative name	CDK Target	Structure
Flavopiridol	Alvocidib, L868275, HMR-1275	1, 2, 4, 6, 7, 9	
TGO2	SB1317, zotiraciclib	1, 2, 7, 9	
P276-00	Roniciclib hydrochloride, P276	1, 4, 9	
Dinaciclib	SCH 727965	1, 2, 5, 9, 12	
Seliciclib	CYC202, Roscovitine	1, 2, 7, 9	
Roniciclib	BAY1000394	1, 2, 4, 7, 9	

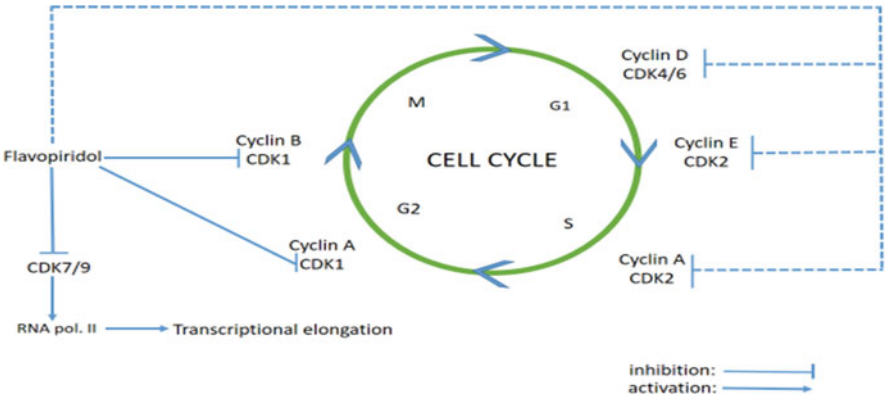


Fig. 13.2 Flavopiridol acting on its target CDK/cyclin complexes

13.3.2 TGO2 (SB1317)

TGO2 is an oral CDK inhibitor which inhibits CDKs including CDK7, CDK2, CDK1, and CDK9 (Fig. 13.3). In pre-clinical studies it has been reported to inhibit glioblastoma cells both alone and in combination (Su et al. 2018). Some studies has

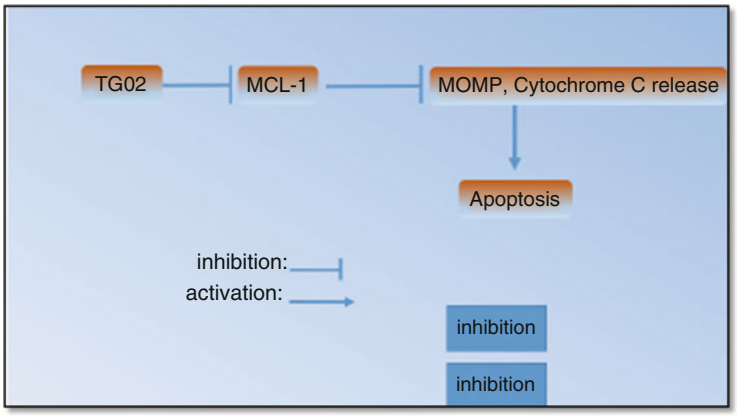


Fig. 13.3 TG02 inducing apoptosis

revealed its activity against hematological diseases and targets a broad range of CDKs and also inhibits JAK/Fit3 activity (Goh et al. 2012). Cultures of cells from AML patients and patients with polycythemia vera are very responsive to TGO2. It has shown positive results against various models of leukemia (Goh et al. 2012, Mehraj et al. 2021a, b, c). Study on patients with AML has shown that TGO2 has inhibitory effect on MCL-1 (inhibitor of apoptosis) and therefore induces apoptosis (Pallis et al. 2017). In addition, in combination TGO2 has shown greater clinical efficacy; for instance, a study has shown that TGO2 when used in combination with carfilzomib (a second-generation proteasome inhibitor) improved the efficacy of refractory multiple myeloma (Ponder et al. 2016).

13.3.3 P276-00

P276-00 is known to inhibit CDK1, CDK4, and CDK9 and has shown activity against cell cycle arrest mostly in the G1 phase and induces apoptosis in the head and neck cancers (Mishra et al. 2013). It has shown anti-tumor activity against mantle cell lymphoma (MCL) cells, with some significant anti-tumor and drug resistant effects in clinical phase II trials. It can repress expression of MCL-1 (anti-apoptotic protein), thereby inducing apoptosis (Shirsath et al. 2012). Research suggests that it has anti-angiogenic activity by inhibiting HIF-1 and lock cancer cells in prostate cancer at G2/M transition (Manohar et al. 2012, Mehraj et al. 2022a, b, c, d). However, the molecular mechanism of P276-00 is not known (Cassaday et al. 2015). Thereby, further verification in this scenario needs further to be evaluated.

13.3.4 Dinaciclib

Dinaciclib is a multi-specific inhibitor inhibiting multiple CDKs such as CDK1, 2, 5, 9, and 12. Dinaciclib mostly obstructs CDK9 activity by preventing the

phosphorylation of the carboxyl terminal of the RNA pol. II that plays a transcriptional inhibitory role and induces apoptosis. FDA in 2012 declared dinaciclib as an orphan drug. Dinaciclib was developed by Merck & Co Ltd. and is under phase III clinical trial. It also inhibits CDK2/5 and anti-apoptotic BCL-XL, BCL-2 proteins. In combo with gemcitabine it robustly inhibited tumor progression of cholangiocarcinoma (CCA) (Saqub et al. 2020). Its anti-tumor activity is p53 dependent. It has shown a significant activity against chronic lymphocytic carcinoma, breast cancer, and lung cancer. However, it has been proven that Dinaciclib has shown strikingly strong efficacy against blood cancers. Dinaciclib mainly acts on leukemic cells and inhibits the growth of T-ALL cells and prolongs the survival of clinical models (Baker et al. 2016). A number of studies have suggested that this drug can abolish several cytokines in the microenvironments like CD40L, IL-4, BAFF, etc., that are crucial for the growth of CLL (chronic lymphocytic leukemia) cells (Mehraj et al. n.d., Johnson et al. 2012). Dinaciclib in combination with panobinostat induces MLL-AF9 tumor cell apoptosis with an increase in the survival rate nearly from 33 days to 52 days (Baker et al. 2016).

13.3.5 Seliciclib (Roscovitine/CYC202)

Seliciclib is actually a multipotent pan-cdk inhibitor highly effective against CDK2, CDK7, and CDK9. Seliciclib is being developed by Cyclacel. It has shown antiproliferative activity against lung cancer, multiple myeloma, and hepatocellular carcinoma. It has been shown in vitro to induce by downregulating anti-apoptotic MCL-1 in lung cancers and others. It mainly inhibits transcription depicting its potency against CDK7/9 (Appleyard et al. 2009).

13.3.6 Roniciclib

Roniciclib is another pan-CDK inhibitor that showed its anti-cancer property on thyroid cancer cell lines (Lin et al. 2018). In phase I clinical trials the effectiveness and tolerability have been tested in patients with advanced malignancy. In addition, it was tested in combination with cisplatin on which it has shown synergistic antitumor activity (Syn et al. 2018). Further combination of sorafenib with Roniciclib has reported to have better growth inhibitory effect on xenograft models than alone (Lin et al. 2018). However, in phase II of clinical trials it has shown serious side effects and cytotoxicity, so its usage was terminated (Cho et al. 2018). Therefore, there is a need to re-optimize Roniciclib for its dosage and administration strategy.

13.3.7 PHA-793887

PHA-793887 has been known to hinder the phosphorylation of Rb protein just to obstruct the cell cycle progression (Locatelli et al. 2010). The in vivo results have

shown promising effects on leukemic cells, xenograft models, and primary leukemic cell dissemination (Alzani et al. 2010). However, in some patients hepatotoxicity was noticed in phase I clinical trials, due to which the clinical application of it is still under development (Massard et al. 2011).

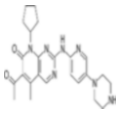
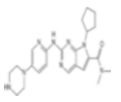
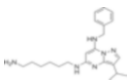
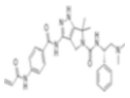
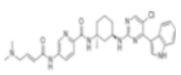
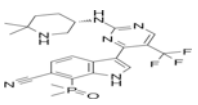
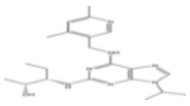
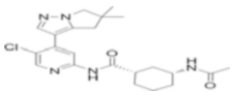
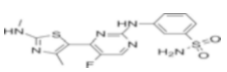
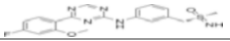
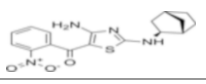
13.4 Specific CDK Inhibitors

The main drawback associated with pan-CDK inhibitors is their little specificity and increased cytotoxicity on normal cell lines. Pan-CDKs were also associated with pharmacokinetic and administration issues. To improve on these things researchers have successfully developed some specific CDK inhibitors that involve CDK4/6, CDK 7, CDK9, CDK12/13 inhibitors, etc. The discovery of flavopiridol opened a raceway for the evolution of molecules with potent and selective CDK inhibition (Sofi et al. 2022a, b). Each cancer type is known to have a specific landscape of CDK expression, therefore specific inhibitors are expected to specifically provide the therapeutic effect. Multiple specific CDK inhibitors have been elucidated in clinical and pre-clinical studies having anti-tumor effects (Table 13.2). Here we will reveal features of some important specific CDK inhibitors and their role in preventing cancer progression.

13.5 CDK4/6 Inhibitors

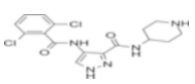
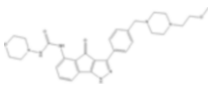
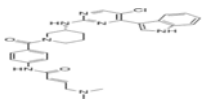
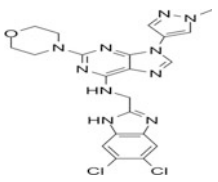
CDK4/6 inhibitors are earliest specific inhibitors that are FDA approved for clinical use. These selectively target CDK4/6 with narrow toxicity to normal cells. They arrest G1/S transition and subsequent cell cycle arrest. These inhibitors mainly target cyclin D-CDK4/6-Rb pathway preventing phosphorylation of Rb (tumor suppressor protein), which is otherwise important for cell cycle progression. CDK4/6 inhibition has improved prognosis in various cancers especially breast cancer subtypes; HR-positive and HER-negative breast cancers. Currently three oral agents are approved by FDA as CDK4/6 inhibitors, namely, abemaciclib, palbociclib, Ribociclib (Kwapisz 2017). These three have been approved to use against breast cancer subtypes especially ER+/HER− in combination with anti-hormone therapy (Mehraj et al. 2022a, b, c, d). Besides similarity as CDK inhibitors, these subtly differ in substrate specificity and pharmacodynamics. Palbociclib almost equally inhibits CDK6 and 4, while ribociclib and abemaciclib are more effective to CDK4 and less to CDK6. Ribociclib and palbociclib have shown prolonged half-life as compared to abemaciclib. Research studies have shown that CDK4/6 inhibitors also suppress cancer growth by bringing on anti-tumor immune responses and senescence regulation of cell metabolism (Deng et al. 2018).

Table 13.2 Specific CDK inhibitors

Name	Alternative name	Target CDK	Structure
Palbociclib	PD-0332991	4, 6	
Abemaciclib	Verzenio	4, 6, 1, 2, 9, 14, 16	
Ribociclib	LEE O11	4, 6	
BS-181		7	
THZ1		7, 12, 13	
YKL-5-124		7	
SY-1365	Mevociclib	7	
SY-5609		7	
Fadraciclib	CYC065	9	
AZD4573		9	
CDKI-73	LS-007	9	
BAY1143572	Atuveciclib	9	
MC180295		9	

(continued)

Table 13.2 (continued)

Name	Alternative name	Target CDK	Structure
AT7519		1, 2, 4, 6, 7, 9	
RGB-286638		1, 2, 3, 4, 5, 6, 7, 9	
THZ531		12	
SR-4835		12	

13.5.1 Palbociclib (PD-0332991)

Palbociclib was the primary CDK4/6 inhibitor to be approved as a cancer therapy. It is a popular CDK4/6 inhibitor sold under brand name Ibrance, developed by Pfizer. In vitro studies have shown that palbociclib is effective against colon cancer, lung cancer, myeloma, and particularly breast cancers (Fry et al. 2004, Qayoom et al. 2021). Rb mutant patients are insensitive to palbociclib treatment, depicting that it has role in blocking phosphorylation of Rb to sequester E2F and thus blocks cell from bypassing restriction checkpoint (Sofi et al. 2022a, b). However, patients taking this drug experience neutropenia (low number of neutrophils). Combination therapeutic approach has always yielded better results. In this case, palbociclib has been used in combination with conventional drugs like tamoxifen, trastuzumab, fulvestrant, paclitaxel, and letrozole against breast cancer subtypes. These combinations and a combination anti-hormone therapy work in a synergistic way to inhibit tumor growth (Malorni et al. 2018) .

13.5.2 Abemaciclib

Abemaciclib, sold under brand name Verzenio, is a medication produced by Eli Lilly and acts as an inhibitor of CDK4/6. It is more potent against CDK4 and has shorter half-life as compared to other CDK4/6 inhibitors (Fig. 13.4). It is a quite different one and inhibits other multiple kinases as well like CDK1/2/5/9/14/16 (Fry et al. 2004). Therefore, it has the ability to stop cell cycle in G1 and G2 as well. Various studies have demonstrated that abemaciclib can also induce tumor regression and tumor cell apoptosis as well. However, abemaciclib is associated with neutropenia

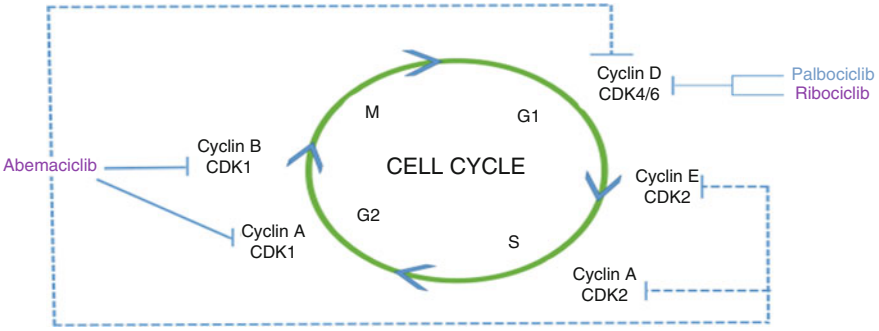


Fig. 13.4 Abemaciclib inhibition on its targets

and GI-toxicities (Rugo et al. 2021). Abemaciclib has shown promising results against cell line deficient in Rb which were resistant to palbociclib and Ribociclib. It is the only specific inhibitor that has been approved for monotherapy against breast cancers.

13.5.3 Ribociclib (LEE O11)

Ribociclib, a CDK4/6 inhibitor, developed by Novartis. It is structurally similar to palbociclib and is used for the treatment of certain breast cancers. Like abemaciclib and palbociclib, it is cytostatic (any agent that slows or stops the growth of cells). It is more powerful against CDK4 than CDK6 like abemaciclib. Neutropenia is associated with its administration. It is used in combination with aromatase inhibitor, letrozole, to antagonize HR+ and HER− breast cancers. Thus, the approved CDK4/6 inhibitors currently trending improved overall survival of breast cancer patients when combined with conventional therapies. Although they all inhibit CDK4/6 but they do differ in substrate specificity, pharmacokinetic properties. Using these drugs in combination therapies might help in reducing side effects (Hortobagyi 2018).

13.6 Specific CDK7 Inhibitors

CDK7 has a bimodal role in progression of cell cycle and transcriptional activation. It is an important component of TFIIH, a general transcription factor, and mediates RNA pol. II phosphorylation at gene regulatory sequences to permit transcription. CDK7 levels are elevated in certain cancers. These findings suggest CDK7 as a potential cancer therapeutic target. Clinical work throughout the world has elucidated number of selective CDK7 inhibitors till date that are in multiple phase trials including LDC4297, BS-181, QS1189, ICEC0942, THZ1, YKL-5-124, THZ2 (Olson et al. 2019).

BS-181 is first specific CDK7 inhibitor with ability to reduce phosphorylation of CDK7 targets thereby inhibiting cell proliferation. But because of its poor cell permeability it has been ruled out of clinical candidature (Ali et al. 2009). Searching for alternatives leads to development of highly selective CDK7 inhibitor ICEC0942. It is an oral cdk7 inhibitor with improved drug properties. Clinically the drug is going through multiple phase trials as monotherapy and in combinatorial approach against prostate cancer, breast cancers, and triple negative breast cancer (TNBC). Its promising pharmacokinetic properties and metabolism make it a good clinical candidate (Patel et al. 2018).

THZ1 is another CDK7 inhibitor with strong anti-tumor and anti-transcriptional activity. It also inhibits activity of CDK12/13 in addition to CDK7. Even research suggests that its anti-tumor activity relies on inhibition of CDK12 and CDK13 (Olson et al. 2019). YKL-5-124 is a potent, highly selective and covalent inhibitor and does not have inhibitory effect on CDK12/13 unlike THZ1. Pre-clinical research studies have demonstrated that YKL-5-124 generates anti-cancer immune response and induces genomic instability (Olson et al. 2019). SY-1365 is another CDK7 selective inhibitor developed by Syros pharmaceuticals derived from THZ. It has entered in phase trials for treatment of ovarian and breast cancers. SY-5609 is another selective CDK7 inhibitor with strong anti-tumor activity, developed by Syros pharmaceuticals. This drug in association with fulvestrant has been approved for clinical trials against TNBC, HR+ and HER2 negative breast cancers. Another CDK7 inhibitor LY3405105 has entered into phase trials against multiple solid advanced tumors.

13.7 CDK9 Inhibitors

CDK9 plays a crucial role in controlling transcription and ensures transcriptional homeostasis. It is normally associated with P-TEFb, a transcriptional elongation factor, modulating gene transcription by phosphorylating C-terminal domain of RNA pol. II. CDK9 dependent phosphorylation is important for processing and maturation of mRNA. CDK9 has been recognized as a valuable target for sorting cancers in which transcription is dysregulated. Moreover, dysregulation of CDK9 pathway has been observed to be associated with various solid and hematological malignancies, making it a valuable anti-cancer target. Functioning of CDK9 has advanced since its discovery and lead to the development of potential molecules as anti-malignants. Numerous selective CDK9 inhibitors have been recognized with strong anti-proliferative property such as AZD-4573, MC180295, CDKI-73, Fadraciclib, etc., some of which have entered clinical development (Borowczak et al. 2022).

Fadraciclib (CYC065), a CDK9 inhibitor with anti-proliferative activity and inhibition of CDK9 mediated transcription (Fig. 13.5). It actually reduces RNA pol. II phosphorylation via CDK9 inhibition and has shown potent anti-tumor activity in multiple cases of malignancies especially neuroblastoma. In addition to CDK9 inhibition, it also inhibits CDK2. Thus, it can also block cell cycle

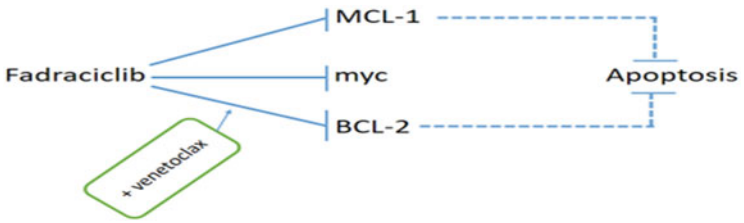


Fig. 13.5 Fadraciclib inducing apoptosis

progression. Fadraciclib represses transcription of Myc oncogene and anti-apoptotic protein Mcl-1. Thus, it may prove beneficial against Triple Negative Breast Cancer (TNBC) in which Myc is over amplified (Poon et al. 2020). Regarding combination therapy, fadraciclib has been used as a combo with other drugs resulting in a more robust anti-tumor response. Like, it has been used with temozolomide against neuroblastoma. Its combination with BCL2 inhibitors including Venetolax has shown promising efficacy against hematological malignancies especially acute myeloid leukemia (AML) (Frame et al. 2020).

AZD4573 is a highly potent selective inhibitor of CDK9 which downregulates anti-apoptotic MCL-1, demonstrating a rapid induction of apoptosis in tumor cells. Although it can block other CDKs as well but its inhibitory effect is many times selective for CDK9. Currently its anti-cancer property is being demonstrated against hematological malignancies (Cidado et al. 2020) .

CDKI-73 is a synthetic CDK9 inhibitor, indirectly represses transcription of E2F via cdk9 inhibition. Thus, blocking G1/S transition. Further research suggests that CDKI-73 exerts pro-apoptotic effect by downregulating anti-apoptotic BCL-2 and MCL-1 via CDK9 inhibition (Borowczak et al. 2022). BAY1143572 (atuveciclib, a benzyl sulfoximine) is another CDK9 inhibitor inhibiting proliferation of cancerous cells even at micromolar concentrations. It reduces RNA pol. II phosphorylation via cdk9 inhibition, lowering transcription of BCL2 and MCL1. Thus, inducing apoptosis also. It has exerted anti-tumor activity against TNBC, lymphomas, esophageal cancers and is currently being investigated in patients with advanced hematological malignancies. NVP-2 is an amino pyrimidine based selective CDK9 inhibitor. It has displayed anti-proliferative activity against certain leukemia's by downregulating MCL-1 and induce apoptosis. 6-bromoindirubin-3'-monoxime is another synthetic CDK9 inhibitor and CDK2 inhibitor. MC180295 is another potent selective CDK9 inhibitor that can reverse the silenced tumor suppressor genes normally silenced during malignancies (Lücking et al. 2017). It also can downregulate myc and MCL1 demonstrating significant anti-cancer activity.

Sangivamycin analogs, also called sangivamycin like molecules (SLM), are nucleoside analogs of anti-tumor and anti-retroviral compound Sangivamycin originally derived from *Streptomyces rimosus*. These analogs possess the same anti-tumor property as demonstrated in pre-clinical study of colon cancer (Cavins et al. 1967). SLM6 is one of the analogs which inhibits CDK9 dependent phosphorylation of RNA pol. II. It can also inhibit CDK1/2, but is more potent against cdk9 as its

inhibition on it results in apoptosis of cancer cells. Another analog SM3 appears to inhibit proliferation of multiple myeloma cells but is neutral toward in malignancies (Borowczak et al. 2022). AAP1742 is another CDK9 inhibitor which decreases RNA pol. II phosphorylation and induces cell apoptosis by downregulating XIAP, BCL-2, and MCL-1. AT7519 is a versatile substance that can inhibit CDK1, CDK2, CDK4, CDK6, CDK7, and CDK9. RGB-286638 is a non-selective inhibitor of CDK1, 2, 3, 4, 5, 6, 7, 9 but increasing potency toward CDK9. It causes robust inhibition of transcription and induction of apoptosis. But its clinical development needs further investigation (Borowczak et al. 2022). SNS-032 is another CDk inhibitor which strongly inhibits CDK9 and weakly inhibits other kinases like CDK2 and CDK7.

Thus, CDK9 inhibitors are broad spectrum inhibitors showing anti-cancer activity by repressing number of anti-apoptotic proteins and downregulating transcription. CDK9 inhibitors may complement current treatment protocols to improve efficacy. Like, these inhibitors have been used in combination therapy with other drugs mainly Doxorubicin, Cyclophosphamide, Rituximab, Bortezomib, BET-inhibitors, etc., just to enhance strength of current treatment regimes. Further most of first-generation CDK9 inhibitors are multipotent targeting multiple CDKs with toxicity. Novel selective CDK9 inhibitors are designed to enhance efficacy and compliance of current treatments. Although there is improvement in treatment efficacy still there are certain pharmacodynamic obstacles that need resolution.

13.8 CDK12 Inhibitors

CDK12 is a transcription related CDK regulating RNA splicing, translation, transcription, and DNA Damage Response (DDR). In association with cyclin k CDK12 regulates transcriptional elongation by phosphorylating RNA pol. II (Blazek et al. 2011). Recently, growing evidences demonstrate involvement of CDK12 in cancers. This may be attributed to its functional role that it does in transcription and other roles. Mutation or anomalic expression of CDK12 has been detected in certain cancers, such as prostate cancer, breast cancer, ovarian cancer, etc. Research suggests that it shows both tumorigenic and tumor suppressive effect. Overexpression of CDK12 in certain cancers lead to malignancy as seen in HER2+ breast cancer, while loss of CDK12 has tumor suppressive effect because of downregulation of DDR genes in this case. Recently, it has been validated as a potential therapeutic target of cancer. In recent years various inhibitors have been developed such as Dinaciclib, THZ1, THZ531, SR-4835, etc.

THZ1 is CDK12/13 and CDK7 inhibitor with strong anti-malignant activity. It inhibits myc oncogene expression and has shown promising results in Ewing Sarcoma, ovarian cancer, and neuroblastoma. THZ531 is a THZ1 based CDK12 inhibitor that damages DNA damage repair pathway (Iniguez et al. 2018). Collaboration of THZ531 with Sorafenib has showed positive results in hepatocellular carcinoma. Dinaciclib is a multi-specific inhibitor inhibiting multiple CDKs including CDK12. It inhibits phosphorylation of RNA pol. II. SR-4835 is another CDK12 inhibitor that downpours DNA Damage repair genes and induces apoptosis. Studies

have shown that loss of CDK12 enhances anti-tumor effect of PARP (Poly-ADP Ribose Polymerase) inhibitors and cell cycle inhibitors checkpoint like Chk1 inhibitor. CDK12 inhibitors in collaboration with PARP inhibitors and Chk1 inhibitor could collaborate to target cancers. Like, combination of PARP inhibitors and SR-4835 has shown synergistic effect in TNBC (Quereda et al. 2019).

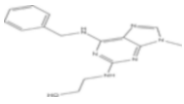
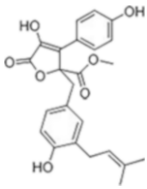
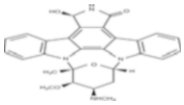
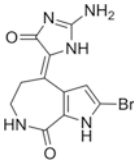
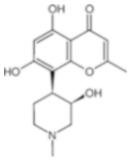
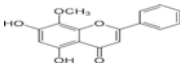
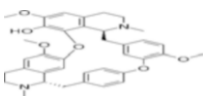
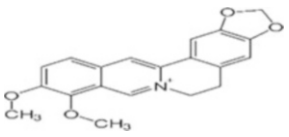
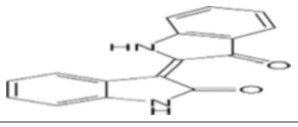
13.9 Natural Compounds Acting as CDK Inhibitors

Natural compounds from marine species, plants, and microorganisms have been recognized as non-specific CDK inhibitors. They lead to discovery of novel compounds with favorable biomedical applications like anti-cancer treatment. Several organisms have been studied as sources of these anti-cancer drugs and have proven effective for destroying tumors in various clinical settings. Here we will reveal some of naturally derived substances from marine species, plants, and microorganisms with CDK inhibitory properties (Table 13.3)**.**

Olomoucine, a derivative of plant cytokinin, is one of the first natural CDK inhibitors obtained from cotyledons of Radish (*Raphanus sativus*). Primarily it was shown to inhibit CDK1 then it was discovered to inhibit CDK2, 5, 7, and 9 also. Olomoucine discovery resulted in the preparation of variety of analogs such as Roscovitine. Roscovitine (Seliciclib) is a synthetic drug inhibiting CDK2/7/9 exhibiting strong anti-proliferative effects (Vermeulen et al. 2002). Butyrolactone-1 is known to inhibit CDK1 and CDK2. It was originally isolated from *Aspergillus terreus*. Butyrolactone-1 arrests both G1 and G2/M along with apoptosis induction (Kitagawa et al. 1994). UCN-01 (7-Hydroxystaurosporine) is a natural CDK1/2 inhibitor isolated from *Streptomyces species*. It arrests cell cycle in G2 by inhibiting Cyclin B-CDK1 (MPF) (Diaz-Padilla et al. 2009). Hymenialdisine lactam is another natural CDK inhibitor derived from *Axinella sp,* a marine sponge. It is an inhibitor of GSK-3B, CDK1/5, MEK-1, and Casein Kinase 1 (Wan et al. 2004).

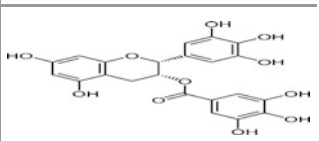
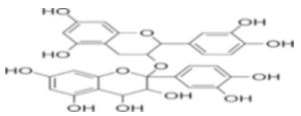
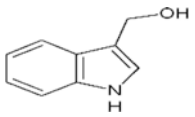
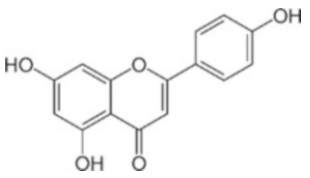
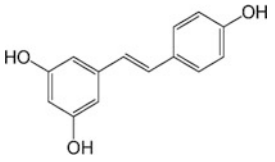
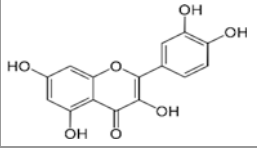
Chromone alkaloids and flavoalkaloids are natural compounds known to have anti-cancer properties. One of the alkaloid Rohitukine isolated from a flowering plant *Dysoxylum binectariferum* led to evolution of Flavopiridol, first pan-CDK inhibitor known to inhibit multiple CDKs [66]. Indirubins are the first natural compounds used by humans as CDK inhibitors. These are derived from gastropod mollusks, indigo-producing plants, and bacteria. Indirubins were principal ingredients of traditional Chinese medication to cure Chronic myelogenous leukemia (CML). Indirubins are renowned inhibitors of CDK1/2 (Kumar et al. 2014). Based on indirubins, synthetic substituted indirubins have been prepared including 6-bromoindirubin and 6-bromoindirubin-3'-monooxime (CDK2/9 inhibitor). Wogonin is a mono-flavonoid natural CDK inhibitor derived from Scutellaria radix. It is known to inhibit CDK2/4 and preferentially CDK9. It reduces transcription of anti-apoptotic MCL-1 by inhibiting CDK9 dependent phosphorylation of RNA Pol. II. Wogonin has shown anti-proliferative properties in experiments on Hodgkin's lymphoma, melanoma, hepatocellular and pancreatic carcinoma. Fangchinoline is an alkaloid based natural CDK inhibitor derived from roots of

Table 13.3 Natural compounds acting as CDK inhibitors

Name	Source	CDK Target	Structure
Olomoucine	*Raphanus*	, 2, 5, 7, 9	
Butyrolactone-1	*Aspergillus terreus*	1, 2	
UCN-01	*Streptomyces species*	1, 2	
Hymenialdisine	*Axinella sp.*	1, 5, GSK-3B, CK1, MEK	
Rohitukine	*Dysoxylum binectariferum*	2, 9	
Wogonin	*Scutellaria radix*	*2, 4, 9*	
Fangchinoline	*Stephania tetrandra*	4, 6	
Berberine	*Berberis spp.*	2, 4	
Indirubin	*Bacteria*	*1, 2, 4, 5*	

(continued)

Table 13.3 (continued)

Name	Source	CDK Target	Structure
EGCG	Green tea	2, 4, 6	
Proanthocyanidin	*Vitis vinifera*	2, 4, 6	
Indole-3-carbinol	Brassicaceae	2, 4, 6	
Apigenin	Fruits and vegetables	2, 4, 6	
Resveratrol	Grapes	2, 4, 6	
Quercetin	Buckwheat	2, 7	

vine plant, *Stephania tetrandra*. It is known to inhibit kinase activities of CDK2, 4, and 6 (Birdsall 1997). Berberine is another alkaloid CDK inhibitor obtained from berberis species. It decreases the levels of CDK2/4.

Triterpenoid compounds called Limonoids including isoobacunoic acid, limonexic acid, isolimonexic acid, and methyl nomilinate derived from citrus species found to have anti-proliferative activity. Methyl nomilinate particularly inhibits CDK4/6 and blocks cell in G1 (Kim et al. 2012). Polyphenols derived from leaf extract of mulberry plant is known to have anti-tumor activity by decreasing activities of CDK4/6/ (Chan et al. 2010). Acetylbritannilactone, a naturally occurring CDK 2/4/6 inhibitor derived from British yellowhead, *Inula britannica*. Flavonoids such as quercetin, isoquercetin, and rutin, from buckwheat seeds and bran downregulate CDK2/7. Polyphenol epigallocatechin-3-gallate (EGCG), a component of green tea causes cell cycle arrest by inhibiting CDK2/4/6 (Shankar et al.

2007). Another polyphenol, namely, Resveratrol derived from grapes well known for its inhibition on cell cycle progression by reducing the levels of CDK2/4 and 6. Proanthocyanidins, from *Vitis vinifera*, have shown to inhibit cell proliferation of epidermoid carcinomas decreasing kinase activities of CDK2/4 and 6. Indole-3-carbinol from Brassicaceae family has shown anti-proliferative activity against colon cancer, endometrial cancer, prostate cancer, and breast cancer. It induces cell cycle arrest by inhibiting CDK2/4/6. Propolis or bee glue is a resinous mixture derived from *Apis mellifera* has shown to inhibit tumor growth by downregulating CDK4. Apigenin, a dietary flavonoid abundant in fruits and vegetables has shown to inhibit tumor growth in mice models. It inhibits CDK2/4/6 (Bailon-Moscoso et al. 2017).

Thus, it is fair to say that naturally occurring compounds derived from plants, microorganisms, and other organisms have tendency to inhibit tumor growth and are modulators of cell cycle regulation. Moreover, there is a certain need of scrutiny of possible targets of these naturally derived compounds and their analogs to increase selectivity and specificity of treatment. To address resistance of tumor cells against these natural compounds a combinatorial approach should be taken. Thus, trials and studies are definite requirements to authenticate clinical approach of these natural compounds either singly or in various combination therapeutic approaches.

13.10 Summary

Cell division is an important aspect and fundamental process of various biological activities including tissue regeneration, homeostasis, pathological processes, various physiological activities, and tumorigenesis. The cell cycle is a succession of events by which a cell duplicates its genome and culminates with the formation of two daughter cells. Cyclin-dependent kinases (CDKs) are key drivers of eukaryotic cell cycle that promote the synthesis of DNA and chromosome segregation by phosphorylation of their substrates. Forfeiture of control over cell cycle is a trademark of cancer. Progression from one phase to next phase of cell cycle requires cyclins and CDKs. Replenishing cell cycle control via CDK inhibition might open some windows for development of targeted cancer therapy. CDKs are not just involved in the cell cycle but also have other important functions, such as insulin production, transcription, neuronal functions, and glycogen synthesis. As CDKs are critical regulators of transcription, cell cycle, and other important biological functions, inhibitors against these CDKs have come into existence to treat multiple malformations associated with CDK dysfunctions. For over 20 years, many compounds have been developed against the abnormally activated CDKs and some are under clinical trials. In this chapter, we have summarized various categories of CDK inhibitors that can be used to treat various malignancies.

Pan-CDK inhibitors are the first generation of CDK inhibitors including Roscovitine and Flavopiridol. The primary role of the pan-CDK inhibitors is to induce cell cycle arrest and hamper cell proliferation by obstructing CDKs activity. Because of their low specificity and toxicity most of the first-generation pan-CDK inhibitors failed in the clinical trials [16–18]. Therefore, second-generation

pan-CDK inhibitors such as RGB-286638, AT519, Dinaciclib, TG02, Roniciclib, P276-00, etc., were developed with improved selectivity and reduced cytotoxicity, and have shown good activity in pre-clinical trials. CDK4/6 inhibitors are earliest specific inhibitors that are FDA approved for clinical use. These selectively target CDK4/6 with narrow toxicity to normal cells. These inhibitors mainly target cyclin D-CDK4/6-Rb pathway preventing phosphorylation of Rb (tumor suppressor protein), which is otherwise important for cell cycle progression. Currently three oral agents are approved by FDA as CDK4/6 inhibitors, namely; abemaciclib, palbociclib, Ribociclib. Specific CDK7 inhibitors like LDC4297, BS-181, QS1189, ICEC0942, THZ1, YKL-5-124, THZ2 are currently recognized as potential inhibitors of CDK7 that inhibit CDK7 induced transcriptional activation. Numerous selective CDK9 inhibitors have been recognized with strong anti-proliferative property such as AZD-4573, MC180295, CDKI-73, and Fadraciclib. Naturally derived substances from marine species, plants, and microorganisms with CDK inhibitory properties such as triterpenoids, olomoucine, proanthocyanidins, and many more.

Thus, numerous synthetic and naturally derived CDK inhibitors have been recognized as anti-tumor drugs that can inhibit the malignancies arising from dysregulation of normal CDKS. Moreover, there is need of scrutinizing more such compounds which will prove effective drugs against different malignancies.

13.11 Further Reading

The readers can further read about "CDK Inhibitors for treatment of breast cancer" by going through the following research papers:

https://onlinelibrary.wiley.com/doi/abs/10.1002/med.1021

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8167670/

For more insights about the topic, we would suggest detailed findings from the books of

(Mir MA, 2022) https://doi.org/10.1016/C2021-0-02565-7, https://doi.org/10.1016/C2022-0-00074-X

(Mir MA, 2021) https://doi.org/10.52305/WXJL6770,

from cancer.net website, https://www.cancer.net/cancer-types/breast-cancer/types-treatment

Readers are advised to look following video lectures for better understanding of this chapter:

https://www.youtube.com/watch?v=BB9jjK7BHkg

https://www.youtube.com/watch?v=vEe3lBduckE

References

Ali S et al (2009) The development of a selective cyclin-dependent kinase inhibitor that shows antitumor activity. Cancer Res 69(15):6208–6215

Alzani R et al (2010) Therapeutic efficacy of the pan-cdk inhibitor PHA-793887 in vitro and in vivo in engraftment and high-burden leukemia models. Exp Hematol 38(4):259–269
Appleyard MVCL et al (2009) Seliciclib (CYC202, R-roscovitine) enhances the antitumor effect of doxorubicin in vivo in a breast cancer xenograft model. Int J Cancer 124(2):465–472
Arellano M, Moreno S (1997) Regulation of CDK/cyclin complexes during the cell cycle. Int J Biochem Cell Biol 29(4):559–573
Bailon-Moscoso N et al (2017) Natural compounds as modulators of cell cycle arrest: application for anticancer chemotherapies. Curr Genomics 18(2):106–131
Baker A et al (2016) The CDK9 inhibitor dinaciclib exerts potent apoptotic and antitumor effects in preclinical models of MLL-rearranged acute myeloid leukemia. Cancer Res 76(5):1158–1169
Birdsall TC (1997) Berberine: therapeutic potential of alkaloid found in several medicinal plants. Altern Med Rev 2:94–103
Blazek D et al (2011) The cyclin K/Cdk12 complex maintains genomic stability via regulation of expression of DNA damage response genes. Genes Dev 25(20):2158–2172
Borowczak J et al (2022) CDK9 inhibitors in multiple myeloma: a review of progress and perspectives. Med Oncol 39(4):1–15
Cassaday RD et al (2015) A phase II, single-arm, open-label, multicenter study to evaluate the efficacy and safety of P276-00, a cyclin-dependent kinase inhibitor, in patients with relapsed or refractory mantle cell lymphoma. Clinical Lymphoma Myeloma and Leukemia 15(7):392–397
Cavins JA et al (1967) Initial toxicity study of sangivamycin (NSC-65346). Cancer Chemother Rep 51(4):197–200
Chan K-C et al (2010) Polyphenol-rich extract from mulberry leaf inhibits vascular smooth muscle cell proliferation involving upregulation of p53 and inhibition of cyclin-dependent kinase. J Agric Food Chem 58(4):2536–2542
Chao S-H et al (2000) Flavopiridol inhibits P-TEFb and blocks HIV-1 replication. J Biol Chem 275(37):28345–28348
Cho BC et al (2018) Phase Ib/II study of the pan-cyclin-dependent kinase inhibitor roniciclib in combination with chemotherapy in patients with extensive-disease small-cell lung cancer. Lung Cancer 123:14–21
Cidado J et al (2020) AZD4573 is a highly selective CDK9 inhibitor that suppresses MCL-1 and induces apoptosis in hematologic cancer CellsAZD4573, a selective CDK9 inhibitor, targets MCL-1. Clin Cancer Res 26(4):922–934
Davidson G et al (2009) Cell cycle control of wnt receptor activation. Dev Cell 17(6):788–799
Deng J et al (2018) CDK4/6 inhibition augments antitumor immunity by enhancing T-cell activation. Cancer Discov 8(2):216–233
Diaz-Padilla I et al (2009) Cyclin-dependent kinase inhibitors as potential targeted anticancer agents. Investig New Drugs 27(6):586–594
Dickson MA (2014) Molecular pathways: CDK4 inhibitors for cancer TherapyCDK4 inhibitors. Clin Cancer Res 20(13):3379–3383
Frame S et al (2020) Fadraciclib (CYC065), a novel CDK inhibitor, targets key pro-survival and oncogenic pathways in cancer. PLoS One 15(7):e0234103
Fry DW et al (2004) Specific inhibition of cyclin-dependent kinase 4/6 by PD 0332991 and associated antitumor activity in human tumor xenografts. Mol Cancer Ther 3(11):1427–1438
Goh KC et al (2012) TG02, a novel oral multi-kinase inhibitor of CDKs, JAK2 and FLT3 with potent anti-leukemic properties. Leukemia 26(2):236–243
Hanahan D, Weinberg RA (2011) Hallmarks of cancer: the next generation. Cell 144(5):646–674
Hortobagyi GN (2018) Ribociclib for the first-line treatment of advanced hormone receptor-positive breast cancer: a review of subgroup analyses from the MONALEESA-2 trial. Breast Cancer Res 20(1):1–11
Iniguez AB et al (2018) EWS/FLI confers tumor cell synthetic lethality to CDK12 inhibition in Ewing sarcoma. Cancer Cell 33(2):202–216
Jiang M et al (2009) Cyclin Y, a novel membrane-associated cyclin, interacts with PFTK1. FEBS Lett 583(13):2171–2178

Johnson AJ et al (2012) The novel cyclin-dependent kinase inhibitor dinaciclib (SCH727965) promotes apoptosis and abrogates microenvironmental cytokine protection in chronic lymphocytic leukemia cells. Leukemia 26(12):2554–2557
Kim J et al (2012) Methyl nomilinate from citrus can modulate cell cycle regulators to induce cytotoxicity in human colon cancer (SW480) cells in vitro. Toxicol In Vitro 26(7):1216–1223
Kitagawa M et al (1994) A cyclin-dependent kinase inhibitor, butyrolactone I, inhibits phosphorylation of RB protein and cell cycle progression. Oncogene 9(9):2549–2557
Kumar N et al (2014) Chebulagic acid from Terminalia chebula causes G1 arrest, inhibits NFκB and induces apoptosis in retinoblastoma cells. BMC Complement Altern Med 14(1):1–10
Kwapisz D (2017) Cyclin-dependent kinase 4/6 inhibitors in breast cancer: palbociclib, ribociclib, and abemaciclib. Breast Cancer Res Treat 166(1):41–54
Lim S, Kaldis P (2013) Cdks, cyclins and CKIs: roles beyond cell cycle regulation. Development 140(15):3079–3093
Lin S-F et al (2018) Activity of roniciclib in medullary thyroid cancer. Oncotarget 9(46):28030
Lin TS et al (2010) Flavopiridol, fludarabine, and rituximab in mantle cell lymphoma and indolent B-cell lymphoproliferative disorders. J Clin Oncol 28(3):418
Locatelli G et al (2010) Transcriptional analysis of an E2F gene signature as a biomarker of activity of the cyclin-dependent kinase inhibitor PHA-793887 in tumor and skin biopsies from a phase I clinical study. Mol Cancer Ther 9(5):1265–1273
Lücking U et al (2017) Identification of atuveciclib (BAY 1143572), the first highly selective, clinical PTEFb/CDK9 inhibitor for the treatment of cancer. ChemMedChem 12(21):1776–1793
Malorni L et al (2018) Palbociclib as single agent or in combination with the endocrine therapy received before disease progression for estrogen receptor-positive, HER2-negative metastatic breast cancer: TREnd trial. Ann Oncol 29(8):1748–1754
Malumbres M, Barbacid M (2009) Cell cycle, CDKs and cancer: a changing paradigm. Nat Rev Cancer 9(3):153–166
Manohar SM et al (2012) Cyclin-dependent kinase inhibitor, P276-00, inhibits HIF-1α and induces G2/M arrest under hypoxia in prostate cancer cells. Prostate Cancer Prostatic Dis 15(1):15–27
Massard C et al (2011) A first in man, phase I dose-escalation study of PHA-793887, an inhibitor of multiple cyclin-dependent kinases (CDK2, 1 and 4) reveals unexpected hepatotoxicity in patients with solid tumors. Cell Cycle 10(6):963–970
Mehraj U et al (2022a) Expression pattern and prognostic significance of baculoviral inhibitor of apoptosis repeat-containing 5 (BIRC5) in breast cancer: a comprehensive analysis. Advances in Cancer Biology-Metastasis 100037:100037
Mehraj U et al (2021a) Tumor microenvironment promotes breast cancer chemoresistance. Cancer Chemother Pharmacol 87:1–12
Mehraj U et al (2021b) The tumor microenvironment as driver of stemness and therapeutic resistance in breast cancer: new challenges and therapeutic opportunities. Cell Oncol 44:1–21
Mehraj U et al (2022b) Adapalene synergistically with doxorubicin promotes apoptosis of TNBC cells by hyperactivation of the ERK1/2 pathway through ROS induction, vol 12
Mehraj U et al (n.d.) Chemokines in triple-negative breast cancer heterogeneity: new challenges for clinical implications. Elsevier
Mehraj U et al (2021c) Prognostic significance and targeting tumor-associated macrophages in cancer: new insights and future perspectives. Breast Cancer 28(3):539–555
Mehraj, U., et al. (2022c). Cryptolepine targets TOP2A and inhibits tumor cell proliferation in breast cancer cells-an in vitro and in silico study. Anti-cancer Agents in Medicinal Chemistry
Mehraj U et al (2022d) Expression pattern and prognostic significance of CDKs in breast cancer: an integrated bioinformatic study. Cancer Biomarkers(Preprint):1–15
Meijer L et al (1997) Biochemical and cellular effects of roscovitine, a potent and selective inhibitor of the cyclin-dependent kinases cdc2, cdk2 and cdk5. Eur J Biochem 243(1–2):527–536
Mir MA et al (2020) Targeting different pathways using novel combination therapy in triple negative breast cancer. Curr Cancer Drug Targets 20(8):586–602

Mishra PB et al (2013) Molecular mechanisms of anti-tumor properties of P276-00 in head and neck squamous cell carcinoma. J Transl Med 11(1):1–11
Morgan DO (1997) Cyclin-dependent kinases: engines, clocks, and microprocessors. Annu Rev Cell Dev Biol 13:261
Olson CM et al (2019) Development of a selective CDK7 covalent inhibitor reveals predominant cell-cycle phenotype. Cell chemical biology 26(6):792–803
Pallis M et al (2017) Complementary dynamic BH3 profiles predict co-operativity between the multi-kinase inhibitor TG02 and the BH3 mimetic ABT-199 in acute myeloid leukaemia cells. Oncotarget 8(10):16220
Patel H et al (2018) ICEC0942, an orally bioavailable selective inhibitor of CDK7 for cancer TreatmentICEC0942, a CDK7 inhibitor for cancer therapy. Mol Cancer Ther 17(6):1156–1166
Ponder KG et al (2016) Dual inhibition of mcl-1 by the combination of carfilzomib and TG02 in multiple myeloma. Cancer Biol Ther 17(7):769–777
Poon E et al (2020) Orally bioavailable CDK9/2 inhibitor shows mechanism-based therapeutic potential in MYCN-driven neuroblastoma. J Clin Invest 130(11):5875–5892
Qayoom H et al (2022) Expression patterns and therapeutic implications of CDK4 across multiple carcinomas: a molecular docking and MD simulation study. Med Oncol 39(10):1–13
Qayoom H et al (2021) An insight into the cancer stem cell survival pathways involved in chemoresistance in triple-negative breast cancer. Future Oncol 17(31):4185–4206
Quereda V et al (2019) Therapeutic targeting of CDK12/CDK13 in triple-negative breast cancer. Cancer Cell 36(5):545–558
Rugo HS et al (2021) Management of abemaciclib-associated adverse events in patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: safety analysis of MONARCH 2 and MONARCH 3. Oncologist 26(1):e53–e65
Saqub H et al (2020) Dinaciclib, a cyclin-dependent kinase inhibitor, suppresses cholangiocarcinoma growth by targeting CDK2/5/9. Sci Rep 10(1):1–13
Shankar S et al (2007) Epigallocatechin-3-gallate inhibits cell cycle and induces apoptosis in pancreatic cancer. Frontiers in Bioscience-Landmark 12(13):5039–5051
Shirsath NP et al (2012) P276-00, a cyclin-dependent kinase inhibitor, modulates cell cycle and induces apoptosis in vitro and in vivo in mantle cell lymphoma cell lines. Mol Cancer 11(1): 1–12
Sofi S et al (2022a) Targeting cyclin-dependent kinase 1 (CDK1) in cancer: molecular docking and dynamic simulations of potential CDK1 inhibitors. Med Oncol 39(9):1–15
Sofi S et al (2022b) Cyclin-dependent kinases in breast cancer: expression pattern and therapeutic implications. Med Oncol 39(6):1–16
Su Y-T et al (2018) Novel targeting of transcription and metabolism in GlioblastomaTG02 in glioblastoma treatment. Clin Cancer Res 24(5):1124–1137
Swaffer MP et al (2016) CDK substrate phosphorylation and ordering the cell cycle. Cell 167(7): 1750–1761
Syn NL et al (2018) Pan-CDK inhibition augments cisplatin lethality in nasopharyngeal carcinoma cell lines and xenograft models. Signal Transduct Target Ther 3(1):1–9
Vermeulen K et al (2002) Antiproliferative effect of plant cytokinin analogues with an inhibitory activity on cyclin-dependent kinases. Leukemia 16(3):299–305
Wan Y et al (2004) Synthesis and target identification of hymenialdisine analogs. Chem Biol 11(2): 247–259
Zeidner JF, Karp JE (2015) Clinical activity of alvocidib (flavopiridol) in acute myeloid leukemia. Leuk Res 39(12):1312–1318
Zhang M et al (2021) CDK inhibitors in cancer therapy, an overview of recent development. Am J Cancer Res 11(5):1913