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REVIEW

Overview of CDK9 as a target in cancer research

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ABSTRACT

CDK9 is a protein in constant development in cancer therapy. Herein we present an overview of the enzyme as a target for cancer therapy. We provide data on its characteristics and mechanism of action. In recent years, CDK9 inhibitors that have been designed with molecular modeling have demonstrated good antitumoral activity *in vitro*. Clinical studies of the drugs flavopiridol, dinaciclib, seliciclib, SNS-032 and RGB-286638 used as CDK9 inhibitors are also reviewed, with their additional targets and their relative IC_{50} values. Unfortunately, treatment with these drugs remains unsuccessful and involves many adverse effects. We could conclude that there are many small molecules that bind to CDK9, but their lack of selectivity against other CDKs do not allow them to get to the clinical use. However, drug designers currently have the tools needed to improve the selectivity of CDK9 inhibitors and to make successful treatment available to patients.

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Introduction

CDK9 was first isolated and designated PITALRE, for the characteristic Pro-Ile-Thr-Ala-Leu-Arg-Glu motif by us.[1] Its chromosomal mapping and phosphorilation sites were studied before it was named CDK9.[2-4] In HIV studies, PITALRE was identified as the catalytic subunit of the positive transcription elongation factor b (P-TEFb), a protein kinase that hyperphosphorylate the carboxyl-terminal domain (CTD) of the large subunit of RNA polymerase II *in vitro*.[5-7] Peng *et al.* are the ones that described P-TEFb as a novel CDK/cyclin pair, calling their subunits CDK9 and Cyclin T for the first time.[8] After that, Cyclin T1, T2a, and T2b were identified. Each binds CDK9 and possesses P-TEFb activity, although 80% of CDK9 binds Cyclin T1, 10% binds T2a, and 10% binds T2b.[9] A year later, Cyclin K was also found to interact with CDK9 *in vivo*.[10] Herein, we provide data of the characteristics and mechanism of action of CDK9. Molecular modeling, *in vitro* and clinical studies of the drugs used as CDK9 inhibitors are also reviewed. Currently, the scientific community requires targeted cancer drugs to get the successful treatment to patients and drug designers have the tools needed to improve the selectivity of CDK9 inhibitors.

Mechanism of action

CDK9 is not a typical Cdc2-like kinase. It does not act in cell-cycle regulation processes; rather, it acts in differentiation processes.[11] It is the catalytic subunit of P-TEFb that, in association with Cyclin T, has the ability to phosphorilate the CTD substrate of RNA polymerase II and reach the RNA transcription elongation.[1-12] Although there are other cyclin-dependent kinases that are capable of phosphorilating the CTD, the only one that activates gene expression in a catalyst manner is CDK9. Therefore, Cyclin T/CDK9 is a dedicated kinase functioning in transcription, with CTD being the major functional target of the complex *in vivo*.[12]

Although the mechanism underlying CDK9 is complex and not totally elucidated, it is schemed and explained in Figure 1. The CTD of the RNA polymerase II comprises tandem repeats of the 7 amino acid sequence YSPTSPS, domain that is essential for the polymerase function *in vivo*.[13] The CTD should be hyperphosphorylated to regulate elongation.[14] The number of phosphorilation sites exceeds 50, serine being the predominant one.[15] There are 2 main phosphorylations carried out by cyclin-dependent kinases (CDKs): the one of Ser5 (YSPT-**Ser5**PS) by CDK7[16,17] and the one of Ser2 (Y**Ser2**PTSPS) by CDK9.[18] Firstly, CDK7 phosphorilates Ser5, allowing for the activation of RNA-Pol II.[18-20] Next, the Ser5 phosphorilated RNA-Pol II is able to stimulate transcription of the RNA, but not its elongation.[20,21] The productive elongation comes with the phosphorylation of Ser2 by P-TEFb.[18,22-26] Therefore, P-TEFb (CDK9/Cyclin T or CDK9/Cyclin K) is essential in order to generate mature mRNAs in cells.

CDK9 Isoforms

There are 2 isoforms of the CDK9 protein: the major 42 kDa CDK9 isoform, and the minor 55 kDa isoform. The 42kDa isoform ($CDK9_{42}$) is the one originally identified as PITALRE.[1] The second form of CDK9 ($CDK9_{55}$) is 13kDa larger than the

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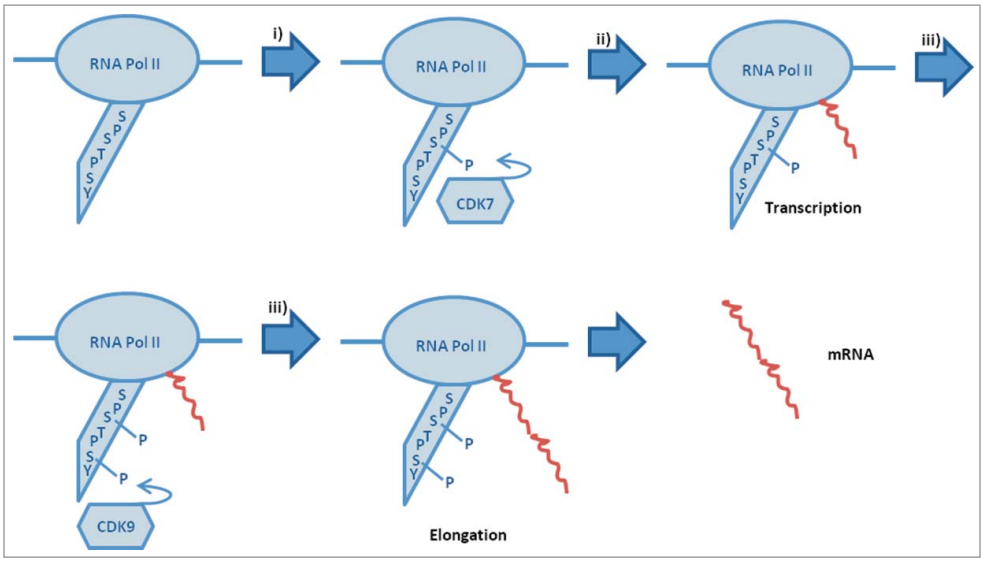


Figure 1. Scheme of RNA-Pol II sequence process: i) activation, ii) transcription and iii) elongation of RNA.

protein originally identified,[27] with a 117 residue terminal extension.[28] Both isoforms were present in HeLa, NIH/3T3 human macrophages and mouse lung and liver tissues, but with different abundance.[28,29] Although their phosphorylation patterns, studied with 144 peptide substrates, are identical, they possess different localization and expression patterns summarized in Table 1.[28,29] These results suggest that the functions of the 2 isoforms should be distinguished, although there is not a concrete characterization of them in literature yet.

$CDK9_{55}$ is identical to $CDK9_{42}$, except for an additional 117 amino acid residues at the amino terminus.[30] The promoter sequence has 2 transcription starts in CDK9. The segment that transcribed $CDK9_{42}$ mRNA is characterized by a GC-rich sequence,[27,31] while $CDK9_{55}$ mRNA is transcribed by a TATA box, that is approximately 500 bp upstream of the mRNA transcription start-point.[24,31] Liu *et al.* found that Ku70, a protein involved in DNA repair, specifically associates with the $CDK9_{55}$, but not with the 42kDa. These results again suggest that the functions of the 2 isoforms should be distinguished, and that $CDK9_{55}$ may play a role in the repair of DNA.

Molecular modeling in CDK9

Medicinal chemistry approaches in drug research and development have evolved alongside the progress observed in molecular modeling drug discovery. The amount of *in silico* studies significantly increased, stimulated by the detailed knowledge of CDK9 at the molecular level and by the advances in bioinformatics.

Table 1. Differences in localization and expression patterns of CDK9 isoforms.[28,29]

	$CDK9_{42}$	$CDK9_{55}$
Localization	Nucleoplasm	Nucleolus
Undifferentiated monocytes	High levels	Not detected
Macrophage differentiation	—	High levels
Primary lymphocytes	Level increased Promoter responsible to activate signals	Level decreased
Promoter in HeLa cells	Strong	—
Hepatocytes	Predominant form after cell cycle	Predominant form before cell cycle

The computational study of the P-TEFb complex allows the identification of several CDK9 inhibitors. Currently, the most prominent method of blocking P-TEFb function is to directly inhibit the ATP-binding site of CDK9 (Fig. 2). Flavopiridol (**1** [Table 2]) is an anticancer drug in phase II clinical trials with a broad specificity, as CDK inhibitor that binds the ATP site of CDK9.[32-35] However, this strategy is not the most specific for drug discovery because the ATP binding pocket is reasonably conserved in the whole CDK family, with more than 12 CDKs involved. Moreover, the inhibitor has to compete with the molecules of ATP during binding, which are in high cellular concentrations.

Alternative approaches have been designed in order to increase the selectivity of CDK9 inhibitors (Fig. 2). One example is done by 5,6-dichlorobenzimidazone-1-β-D-ribofuranoside (DRB). It blocks the ATP binding site of CDK9 by halogen bond formation, inducing conformational changes in the glycine-rich loop of CDK9. This change of conformation contributes to a high affinity interaction.[36] The pan-CDK inhibitor CR8 (**2** [Table 2]) induces a downward movement of this loop in CDK9.[37] The importance of halogen atoms in the molecular design of selective CDK9 inhibitors is reinforced by the discovery of the indirubin-3′-monoxime derivative (**3**) showed in Table 2.[38] 5-Fluoro-N^2,N^4-diphenylpyrimidine-2,4-diamines (**4** [Table 2]) binds the ATP binding site of CDK9 with a different orientation from that of flavopiridol.[39] However, the CDK9 inhibition by all these molecules (**2–4**) is lower than the one done by flavopiridol (**1**).

The study of the interactions of a series of substituted 4-(thiazol-5-yl)-2-(phenylamino)pyrimidines (**5**, Table 2) and of CAN508, a 4-arylazo-3,5-diamino-1*H*-pyrazole inhibitor, with the ATP binding site of CDK9 and CDK2 suggests that the ATP binding site of CDK9 is more malleable than that of CDK2 (Fig. 2), and can accommodate large and flexible

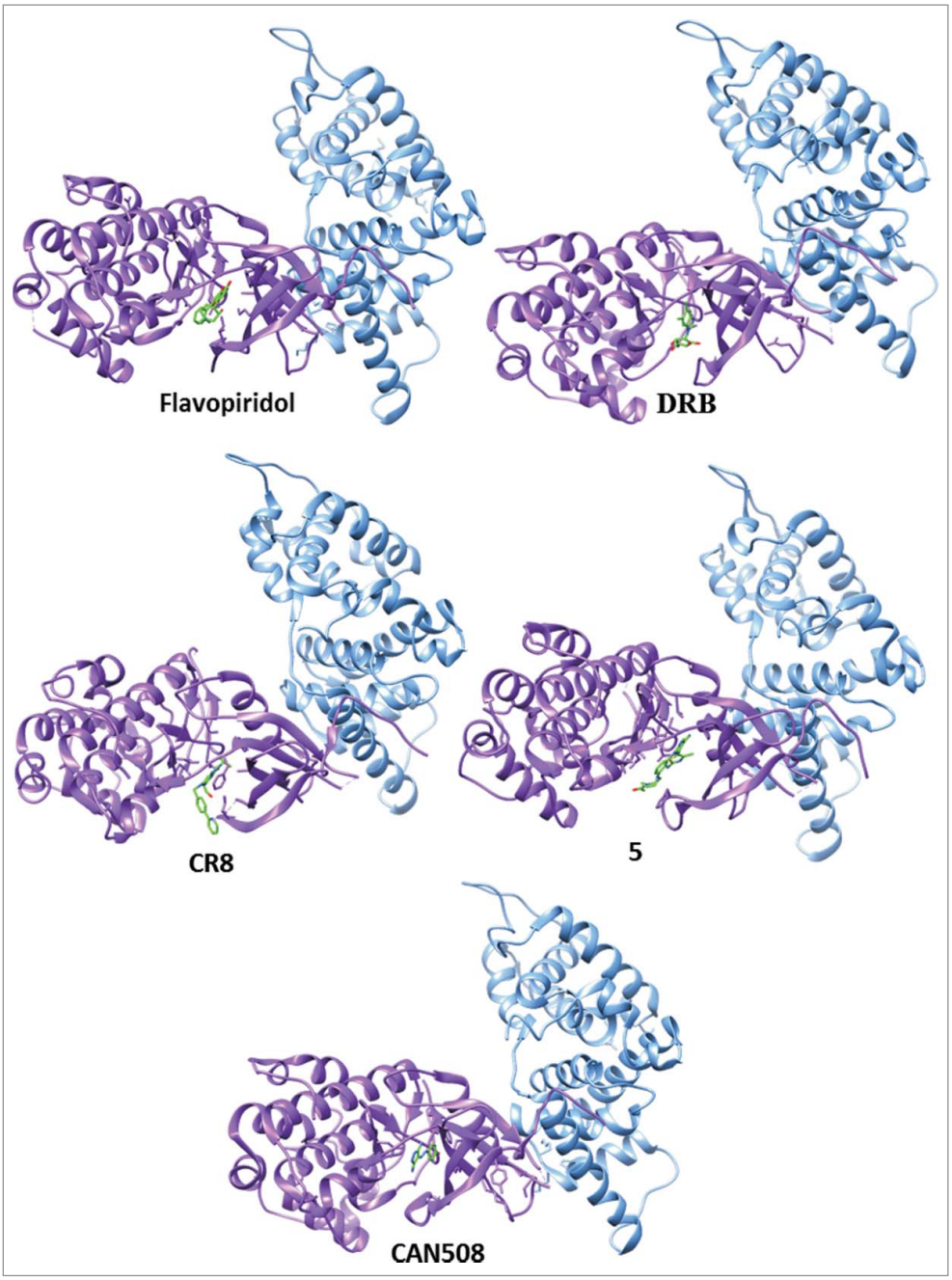


Figure 2. CDK9 inhibitors blocking the ATP-binding site (CDK9 is in purple and Cyclin T1 in blue).

compounds.[40-42] These studies provide another approach for the selectivity of inhibitors toward CDK9 over CDK2.

Another example is the computational study of the CDK9/cyclin T1 protein-protein interaction done by Randjelovic *et al.*,[43] where 2 peptide sequences were identified as potential inhibitors to bind the surface of CDK9. In this way, they directly interfere with the CDK9/Cyclin T1 complex formation. Furthermore, the small molecule 2-amino-8-hydroxyquinoline has been proposed as a potential inhibitor of the CDK9/Cyclin T1 interaction.[44]

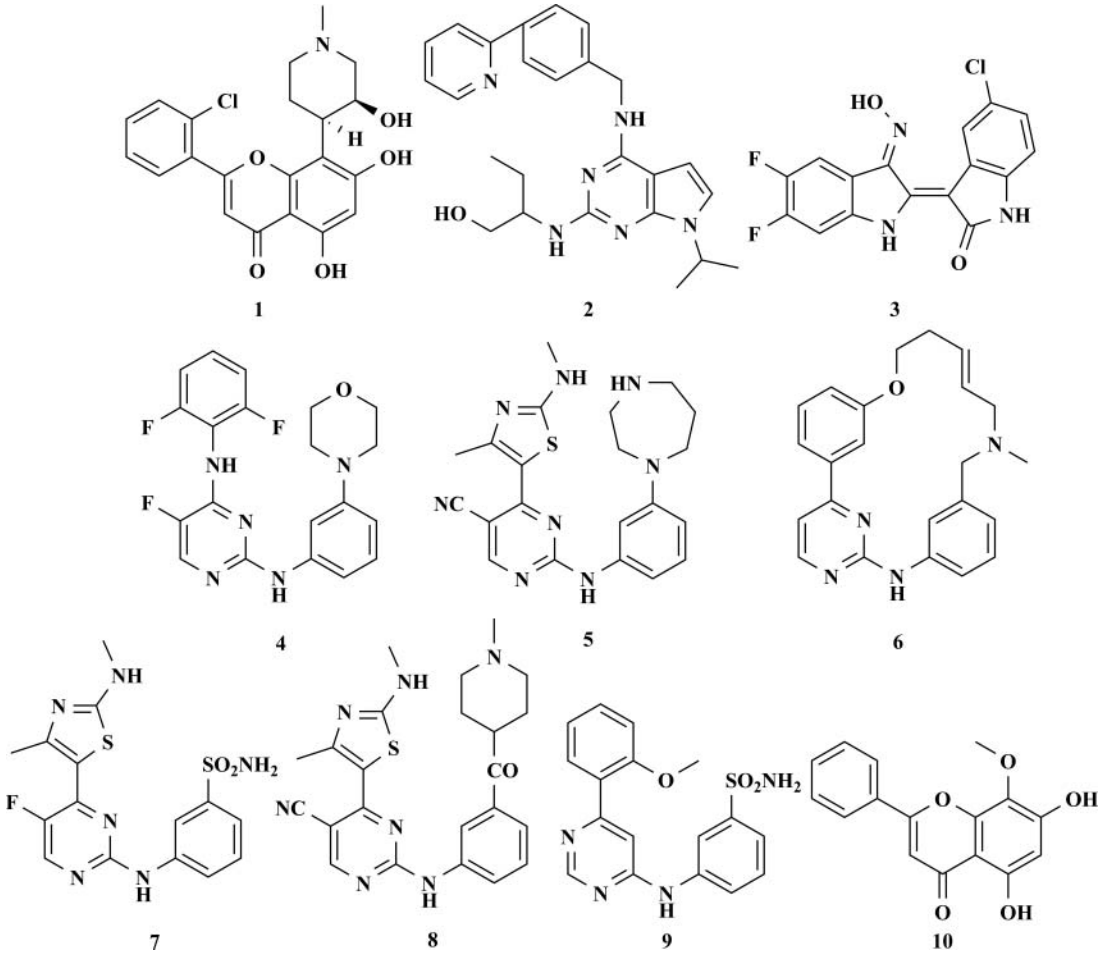
F07 and F07#13 are 2 small molecules that despite being studied as anti-retroviral drugs, target the interface pocket of CDK9/Cyclin T1. The *in silico* analysis of *Duyne et al.* demonstrated a better binding by the drugs to the active form of CDK9.[45]

Small Molecules as CDK9 Inhibitors

Research in small molecules is fundamental for the discovery of a successful drug in targeted cancer treatment. Herein, we summarize some of the small molecules that have been designed as antitumor drugs with CDK9 inhibition (Table 2).

TG02 (**6** [Table 2]) is one of the molecules with the best value of CDK9 inhibition K_1 (3nM).[46] However, it has not been designed as a CDK9 inhibitor specifically, as it also binds other kinases, such as Janus Kinase 2 and Fms-like tyrosine kinase-3.[47] TG02 is a macrocycle that holds a phenylamino pyrimidine as CDKI-73 (**7**) and the 2,4,5-trisubstited pyrimidine derivative (**8**) showed in Table 2. These molecules have shown appreciable selectivity for CDK9 as CDK inhibitors, capable of activating caspase 3, reducing the level of Mcl-1 anti-apoptotic protein,

Table 2. CDK9 Inhibition K_1 values by small molecules 1–10.



Number	Name	Inhibition K_1 (nM)
1	Flavopiridol[39]	4.59
2	CR8[37,53]	110
3	Indirubin-3′-monoxime derivatives[38]	400
4	5-Fluoro-N^2,N^4-diphenylpyrimidine-2,4-diamines[39]	330
5	4-(thiazol-5-yl)-2-(phenylamino) pyrimidines[40,50]	7
6	TG02[48,49,54]	3
7	CDKI-73[48]	4
8	2,4,5-trisubstited pyrimidine derivatives[49]	14
9	LCD000067[51]	44
10	Wogonin[52]	190

and inducing cancer cell apoptosis in breast, colon and leukemia cancer cells.[48,49]

Other CDK inhibitors with the phenylamino pyrimidine in their structure that bind the ATP binding site and present CDK9 potency and selectivity are LDC000067 (**9** [Table 2]) and the substituted 4-(thiazol-5-yl)-2-(phenylamino) pyrimidine (**5** [Table 2). They have demonstrated potent anticancer activity against different cell lines, such as cervix, lung, breast and leukemia with down-regulation of Mcl-1.[50,51] These small molecules holding a phenylamino pyrimidine could represent promising leads for the development of specific CDK9 inhibitors.

Wogonin, one of the active flavones from the natural herb *Scutellaria balcalensis*, should be highlighted as a CDK9 inhibitor (**10** [Table 2]). It presents similarities with the structure of flavopiridol, and blocks the phosphorylation of the carboxy-terminal domain of RNA polymerase II at Ser2, resulting in apoptosis induction in leukemic T-cells *in vitro*.[52]

It should be considered that, although the search of the most specific CDK9 inhibitor is depicted, the activity of these inhibitors toward other kinases is not necessarily detrimental. The final judgement on the anticancer potential of a molecule should go through *in vivo* experimentation inescapably, where the overall therapeutic efficacy can be evaluated.

Table 3. CDK9 Inhibitors in Clinical Trials.

Name	Additional Targets	Clinical Trials		
		Phase	Tumors*	IC_{50} (nM)**
Flavopiridol	CDK1, CDK2, CDK4, CDK6, CDK7, CDK9, GSK3β[35,83]	II	AML[56]; PPC[57]; CLL[58]	AML: 400[84]; Ov202: 100[85]; B-CLL: 100[86]
		I	RMM[64]; NHL[65]; CLL[63,69]; AML[70]; ALL[70]; ABLs[70]	U266: 10[87]; RPMI-8226: 10[87]; JeKo-1: 70[88]; Molt-4: 100[89]; K562: 350[89]
Dinaciclib	CDK1, CDK2, CDK5, CDK9[83,89]	II	ABC[71]; NSLC[72]; AML[73]; ALL[73];	Breast: 8[90]; Lung: 6–14[90]; Leukemia: 6[90];
		I	CLL[74]; RMM[76]	J558: 2[91]
Seliciclib	CDK1, CDK2, CDK5, CDK7, CDK9, CK1, GSK3A, DIRK1A,ERK1[83]	I	SAT[78,79]	Mean: 7400[92]
SNS-032	CDK1, CDK2, CDK4, CDK7, CDK9[83]	I	SAT[80]; CLL[81]; RMM[81]	Leukemia:139[93]
RGB-286638	CDK1, CDK2, CDK4, CDK5, CDK6, CDK7, CDK9[82,83]	I	SAT[82]	Myeloma: 100[94]

*AML: Acute myelogenous leukemia; PPC: Primary peritoneal carcinoma; CLL: Chronic lymphocytic leukemia; RMM: Relapsed multiple myeloma; NHL: Non-Hodgkin's lymphoma; ALL: Acute lymphoblastic leukemia; ABLs: Acute byphenotypic leukemias; ABC: Advanced breast cancer; NSLC: Non-small cell lung cancer; SAT: Solid advanced tumors.

**Half maximal inhibitory concentration of each drug against the cell lines indicated and expressed in nM.

Clinical Trials of CDK9 Inhibitors

Randomized controlled trials are considered the most reliable methodology for acquiring adequate data to understand the benefits and risks of new drugs and how they are optimally utilized.[55] Five CDK9 inhibitors that have been tested in clinical trials in the last years are reviewed in this paper, with additional data about the specific tumoral pathologies involved in each trial, their additional targets and their relative IC_{50} values listed in Table 3.

Flavopiridol is the drug most often evaluated in clinical trials as a CDK9 inhibitor. A randomized phase II study of 2 schedules of flavopiridol given with cytosine arabinoside and mitoxantrone to patients with acute myelogenous leukemia (AML) garnered 58% complete response, although 8% of the patients left the study because of the adverse effects and 13% of them died.[56] The complete response to the treatment in the other 2 phase II trials was approximately 2%. One of the studies observed combination with cisplatin in primary peritoneal carcinoma (PPC),[57] while the other was only of flavopiridol in patients with leukemia.[58] In this last study, all patients suffered adverse effects, with 87% high risk. It should be mentioned that 26% of the patients stopped the treatment with flavopiridol due to an adverse event.[58]

There is no complete response in 7 of the 12 flavopiridol clinical trials in Phase I studied.[59-65] Many adverse effects and events were described in the trials, such as thrombocytopenia,[59,60,63,64] embolism,[60] neutropenia[60,62-65] and fatigue.[59,61,65] Therefore, more than the half of the Phase I studies did not satisfy the patients. In addition, there are only 3 studies with complete response under 10%,[66-68] and one where 3 of the 9 patients had complete remission, but 8 presented anemia.[69] The study where the percentage is higher is the one which observed the association to cytosine arabinoside and mitoxantrone mentioned before (40%), although 51% of the patients suffered tumor lysis syndrome.[70]

Dinaciclib is the other CDK9 inhibitor that has been featured in Phase I and II clinical trials throughout the last years. In three Phase II studies where it was involved, there was not a complete response to the treatment and 75–95% of the patients suffered adverse effects.[71-73] Moreover, Phase I studies of the drug revealed several adverse effects and no complete response in any case.[74-77]

Yet another CDK9 inhibitor involved in Phase I studies is seliciclib. Although the clinical trials do not reveal many adverse effects, they also do not expose any complete response by the patients treated.[78,79] A Phase I study enrolling SNS-032, a CDK 2, 7 and 9 inhibitor, was terminated during dose-escalation. 100% of the patients suffered clinical adverse effects.[80] Other Phase I and pharmacologic study of the drug demonstrated that there is no response to antitumor activity in the patients, with 75% having adverse effects.[81] RGB-286638, a novel multitargeted CDK inhibitor, including CDK9, revealed no complete response to the treatment and 23% adverse effects described by the patients in its first human trial.[82]

It should be mentioned that these aforementioned 5 inhibitors used in clinical trials (flavopiridol, dinaciclib, seliciclib, SNS-032, RGB-286638) are not selective to CDK9. They also inhibit other CDKs and other enzymes (Table 3). Therefore, unsuccessful treatment with these drugs involving many adverse effects could be due to its lack of selectivity.

Conclusion

CDK9 is a target in constant development in cancer therapy. CDK9 inhibitors have demonstrated good antitumoral activity *in vitro*. Although there are many small molecules that bind CDK9, the lack of selectivity against other CDKs and enzymes does not allow their clinical use. However, drug designers have the tools required to improve the selectivity of CDK9 inhibitors. Moreover, the scientific community requires targeted cancer drugs to offer patients successful treatment.

Disclosure of potential conflicts of interest

The authors confirm that the content in this article presents no conflict of interest.

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