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REVIEW

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CDK7 as a New therapeutic target in pancreatic and lung cancer: current evidence and future perspectives

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ABSTRACT

Introduction: Cyclin-dependent kinase 7 (CDK7) is a key regulator of transcription and the cell cycle, with its dysregulation linked to tumorigenesis and chemoresistance. CDK7 serves as an unfavorable prognostic marker in multiple cancers and is significantly overexpressed in patients with poor prognosis, including those with lung and pancreatic cancer.

Areas covered: This review explores the role of CDK7 in tumorigenesis, focusing on transcriptional regulation, tumor metabolism, and therapy resistance. The development of CDK7 inhibitors has gained attention as a potential strategy to overcome chemoresistance. Notably, cancer cells exhibit sensitivity to CDK7 inhibitors at doses well tolerated by normal cells, supporting their clinical applicability. This review examines key CDK7 inhibitors, including THZ1, LDC4297, and YKL-5-124, in non-small-cell lung cancer (NSCLC), small-cell lung cancer (SCLC), and pancreatic ductal adenocarcinoma (PDAC), highlighting their mechanisms and therapeutic potential. Resistance mechanisms and combination strategies with chemotherapy, targeted therapies, or immunotherapy are also discussed.

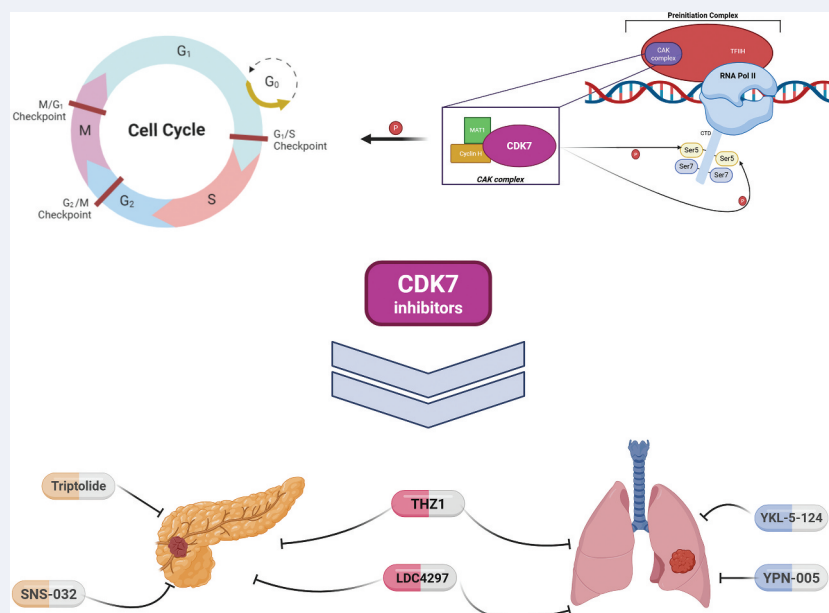
Expert opinion: Despite promising preclinical results, challenges remain, including specificity, biomarker identification, and clinical validation. Further research is needed to optimize dosing, address resistance, and translate CDK7 inhibitors into clinical practice. Lastly, ongoing and future clinical trials will be essential to determining their therapeutic potential in PDAC, NSCLC, and SCLC.

ARTICLE HISTORY

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Role of CDK7 and specific inhibitors in PDAC and Lung Cancer. At the top, the CDK-activating kinase (CAK) complex regulates the cell cycle and transcription through CDK7. At the bottom, the main CDK7 inhibitors tested in pancreatic and lung cancer are shown in relation to their respective cancers. Created in BioRender. Rocco, M. (2025) [div https://BioRender.com/q51ydkc](https://BioRender.com/q51ydkc).

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Article highlights

- CDK7 plays a key role in transcription regulation and cell cycle control, making it a promising therapeutic target in cancer.
- Overexpression of CDK7 is associated with poor prognosis in several malignancies, including nscl.
- CDK7 inhibitors, such as THZ1, LDC4297, and YKL-5-124, have shown significant antitumor activity in preclinical models.
- Combining CDK7 inhibitors with chemotherapy, targeted therapy or immunotherapy enhances therapeutic efficacy and overcomes resistance.
- Despite promising preclinical data, further clinical studies are required to validate CDK7 inhibitors as a standard treatment strategy.

1. Introduction

Cyclin-dependent kinases (CDKs) are serine/threonine kinases dependent on a regulatory subunit, a cyclin, for activation. Based on the kinase domain they are divided into several classes. They are characterized by dependence on specific regulatory protein subunits, such as cyclins, which activate their enzymatic activity by providing the structural sequences necessary for proper functioning of the catalytic site [1].

CDKs are involved in the cell cycle and other cellular processes, such as gene transcription, insulin secretion, glycogen synthesis and neuronal functions. In particular, CDK7 is one of the main regulators of cell cycle progression and gene transcription [2]. Its overexpression has been observed in several cancers, including breast cancer, hepatocellular carcinoma, gastric cancer, colorectal cancer, squamous cell carcinomas of the oral cavity, head and neck and esophageal cancers, as well as ovarian cancer [3]. For these reasons, CDK7 has been investigated as a potential target for anticancer drugs. Notably, high CDK7 levels have been linked to poor prognosis in two of the deadliest cancers: lung cancer [4] and pancreatic ductal adenocarcinoma (PDAC) [5]. In 2022, lung cancer was the most frequently diagnosed cancer, with 2.5 million cases, and remained the leading cause of cancer-related death, accounting for an estimated 1.8 million deaths [6]. Lung cancer is classified into two main types: small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC). Survival rates vary depending on the stage at diagnosis; however, lung cancer is often detected at an advanced stage, with 30%–40% of NSCLC cases and approximately 60% of SCLC cases diagnosed at stage IV [7].

SCLC accounts for approximately 15% of cases and is the most aggressive form of lung cancer [8]. It is a neuroendocrine tumor characterized by dense layers of small cells with sparse cytoplasm, fine and granular nuclear chromatin, and a high mitotic index. Notably, it expresses neuroendocrine markers [7]. SCLC has a rapid onset, and although chemotherapy is initially effective, relapse occurs quickly in most cases, often with metastases to the brain, liver, adrenal glands, bones, and bone marrow [9]. Consequently, the 5 years overall survival rate remains below 7% [8]. Currently, there are no established prognostic or predictive biomarkers to guide therapeutic decision-making [8]. It has been observed that the concomitant inactivation of the tumor suppressors *p53* and *RB* is required

for tumorigenesis in the majority of patients [10]. These events typically occur in lung neuroendocrine cells expressing Achaete-Scute Homolog 1 (ASCL1), which are predominantly located in the larger airways, and trigger the molecular mechanisms necessary for tumor development. However, while SCLC mainly originates from pulmonary neuroendocrine cells, in rare cases, it can also arise from epithelial cells such as alveolar type 2 cells, basal cells, or club cells [11]. NSCLC accounts for 85% of lung cancers and is further classified into lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), and large cell carcinoma (LCC) [7]. Significant advances in personalized therapeutic approaches have been made in recent years for this type of cancer [3]. However, despite these advances, the disease is diagnosed at a metastatic stage in the majority of patients, leading to poor prognosis and high recurrence rates after treatment [4]. Genomic profiling has improved the understanding of the underlying molecular mechanisms, enabling the development of molecularly targeted therapies. To date, surgery remains the treatment of choice for localized NSCLC cases [7]. For patients with advanced disease, several treatment options are available, with molecular profiling routinely performed to guide therapeutic decisions. Mutations in the *EGFR*, *ALK*, *BRAF*, *HER2*, *MET*, *RET*, *ROS1*, and *neurotrophic receptor tyrosine kinase (NTRK)* genes have been shown to predict responses to targeted therapies, which are predominantly administered to LUAD patients, who are typically younger and non-smokers [12]. For advanced-stage patients, platinum-based chemotherapy in combination with immunotherapy is the preferred approach [7]. PDAC is one of the leading causes of cancer-related death worldwide, and by 2030, it is expected to become the second leading cause of cancer-related death in the U.S.A. [13]. Currently, the 5-year survival rate after diagnosis is around 10% [14,15]. The main causes of mortality in PDAC are late diagnosis, often at a metastatic stage [16] because of the absence of specific biomarkers for early detection and resistance to current therapy approaches [15]. Only a minority of patients are treated with surgical resection, which is not always successful [17], while most receive chemotherapy, though resistance often develops [18]. Some hereditary genetic mutations in *BRCA1*, *BRCA2*, *ATM*, *MLH1*, and *MSH2* can increase the likelihood of developing PDAC during one's lifetime [19]. However the main mutations identified in patients with PDAC are at the *KRAS* level; these mutations inhibit its GTPase activity [20], *KRAS* is also involved in gene transcription, and the aberrant signaling of *KRAS*, mainly mediated by the ERK pathway, drives cancer growth in PDAC [21], *KRAS* mutations are often associated with poor prognosis [22]. Currently, therapeutic strategies in PDAC primarily involve the FOLFIRINOX and gemcitabine–nab-paclitaxel combined regimens. However, these treatments are often ineffective in patients, with limited improvements in terms of reducing metastases or increasing survival [23,24].

2. Cyclin-dependent kinase 7 (CDK7)

CDKs are serine/threonine kinases that require a regulatory subunit, a cyclin, for their activation. CDKs belong to the Cyclin-dependent kinases, Mitogen-activated protein kinases, Glycogen synthase kinase 3, and CDK-like kinases

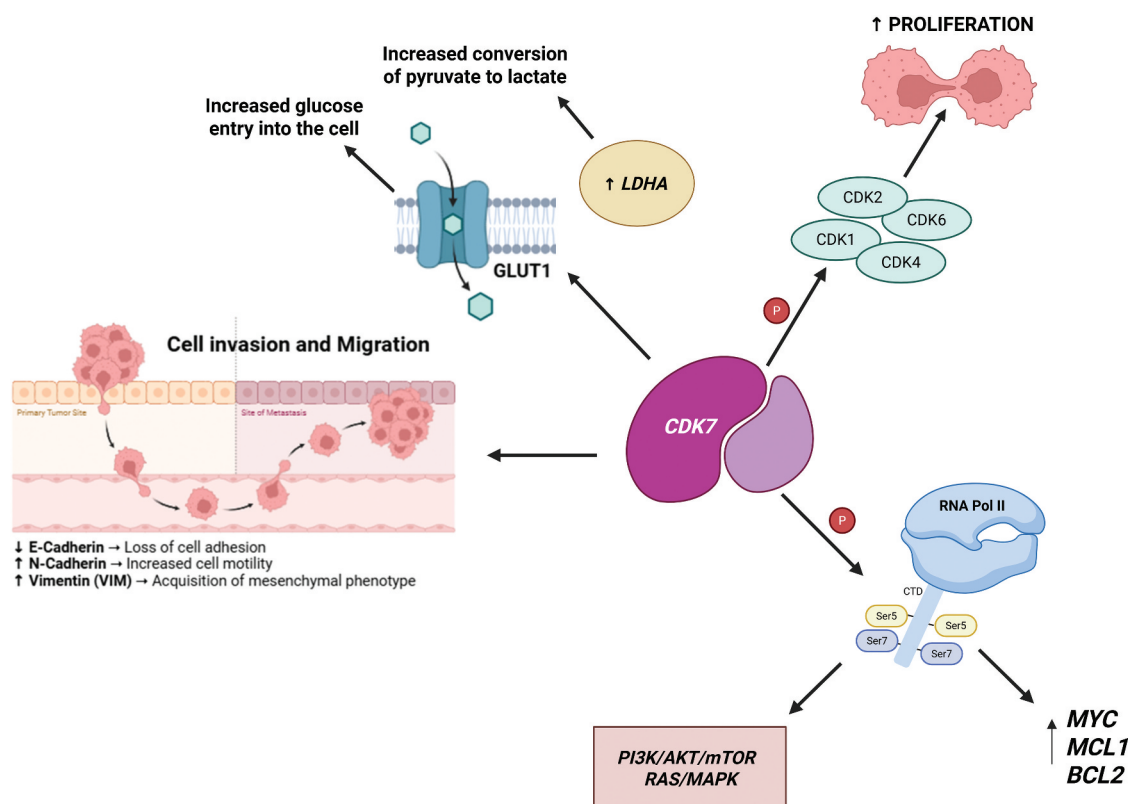


Figure 1. Schematic representation of CDK7 involvement in key oncogenic process, including cell proliferation, transcription regulation, activation of oncogenic pathways, cell migration and glucose metabolism. Created in BioRender. Rocco, M. (2025) <https://BioRender.com/16t5hih>.

(CMGC), which also includes Mitogen-Activated Protein Kinases (MAPKs), Glycogen Synthase Kinase 3 (GSK3 β), members of the Dual Specificity Tyrosine-Regulated Kinase (DYRK) family, and CDC-like kinases [1]. As previously mentioned, CDKs are typically activated through binding to a cyclin and phosphorylation of the T-loop by an activator kinase, known as the CDK-activating kinase (CAK). CAK is a trimeric complex composed of CDK7, cyclin H, and the RING-finger protein MAT1 [25]. Thus, CDK7 is part of the CAK complex, which, in turn, is part of the Transcription Factor IIH (TFIIH) complex [26]. CDK7 is a kinase protein that regulates cell cycle progression and, unlike other CDKs, also controls gene expression, insulin secretion, glycogen synthesis, and neuronal functions [2,27]. This makes CDK7 a key regulator of both transcription and cell cycle progression, with significant implications in tumor progression when CDK7 is aberrantly active [2,26,28]. The structure of CDK7 consists of two main lobes: an N-terminal lobe containing β sheets and an α helix (α C) and a C-terminal lobe, primarily formed by α helices. ATP is bound between the two lobes. The sequence NRTALRE is exposed and does not interact with ATP, as it does in other active kinases. The activation segment is visible, but it exhibits greater flexibility compared to the rest of the structure [29]. CDK7 is essential for cell proliferation and cell cycle activation [30] through autophosphorylation of Thr170 in the T-loop and binding to cyclin H. It also has a second phosphorylation site, Ser164, which makes it more akin to cyclin H. These two residues are phosphorylated by both CDK1 and CDK2 [25,31]. Its

involvement in the cell cycle stems from its ability to phosphorylate the kinases CDK1, CDK2, CDK4, and CDK6, all of which are crucial for the different phases of the cycle. Its activity regulates the temporal sequence of cyclin appearance, ensuring proper cell cycle progression [25]. CDK7 plays a crucial role in multiple steps of transcription. During the initiation phase, as a component of the TFIIF complex, it phosphorylates the Ser5 residue in the Carboxy-Terminal Domain (CTD) of RNA polymerase II (RNAPII). This phosphorylation facilitates the transition from transcription initiation to elongation, enabling productive RNA synthesis [2,28]. It is also subsequently involved in the regulation of other transcription factors, which participate in the assembly of the pre-initiation complex (PIC) through a process known as promoter escape [31] (Figure 1).

2.1. CDK7 in cancer

Dysregulation of several protein kinases is associated with carcinogenic processes and chemoresistance [32]. CDK7 is dysregulated in many types of cancer and has been found to be significantly elevated in patients with poor prognosis [5]. In addition, CDK7 expression is positively associated with upregulation of the PI3K/AKT/mTOR pathway resulting in increased tumor growth, drug resistance, and epithelial-to-mesenchymal transition (EMT) [33].

The synthesis and development of CDK7 inhibitors are gaining increasing attention and are emerging as a potential therapeutic strategy to overcome chemoresistance in various

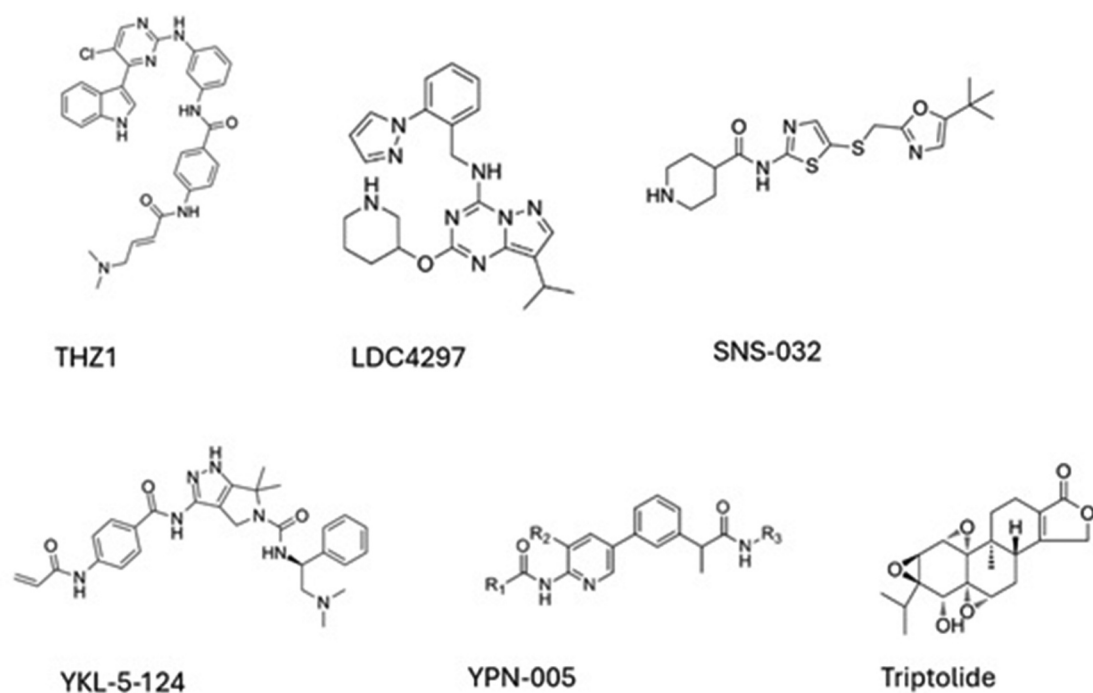


Figure 2. Chemical structure of CDK7 inhibitors.

Table 1. List of CDK7 inhibitors, including information on mechanism of action, specificity, stage of preclinical or clinical development, tumor types in which they have been tested and combinations explored in therapeutic studies.

Drug Name	Models	Cell line tested	Trial status	Mechanism	Drug(s) used in the combination	References
THZ1	PDAC NSCLC SCLC	A549 H1975 H460 HCC827 H520 H1703 HCC95 H1299 H292 H23 H3122 STE-1 RP-GEM	Pre-clinical phase	Irreversible nonselective covalent inhibitor	Gemcitabine Paclitaxel Topotecan Anti-PD-1 immunotherapy	[2,4,32,42,44,46,47,50]
LDC4297	PDAC NSCLC	MIA PaCa-2 Panc89 PT45 BxPC3 A549 H1975	Pre-clinical phase	Competitive inhibitor	Palbociclib	[28,41]
YKL-5-124	SCLC	GLC16, DMS79, NCI-H69, NCI-H82 SCLC <i>Rb1</i> ^{-/-} <i>p53</i> ^{-/-} <i>p130</i> ^{-/-} (RPP)631, <i>Rb1</i> ^{-/-} <i>p53</i> ^{-/-} (RP) RPP-MYC cells	Pre-clinical phase	Reversible selective inhibitor	PD-1 inhibitor	[43]
SNS-032	PDAC	PancVH1 HPNE	Pre-clinical phase	Nonselective inhibitor that binds CDK2, CDK7 and CDK9	TRAIL	[55]
YPN-005	SCLC	H209 H82 H69 Mouse models	Pre-clinical phase	Non-covalent inhibitor		[45]
Triptolide	PDAC	MIA PaCa-2 PANC-1	Phase I			[55]

types of cancer. Additionally, tumor cells are sensitive to CDK7 inhibitors at doses to which healthy cells are insensitive, suggesting that the treatments could be well tolerated in a clinical setting [34]. In vitro and in vivo studies have shown that CDK7 inhibition led to reduced mRNA synthesis and decreased RNAPII recruitment to gene promoters, suggesting

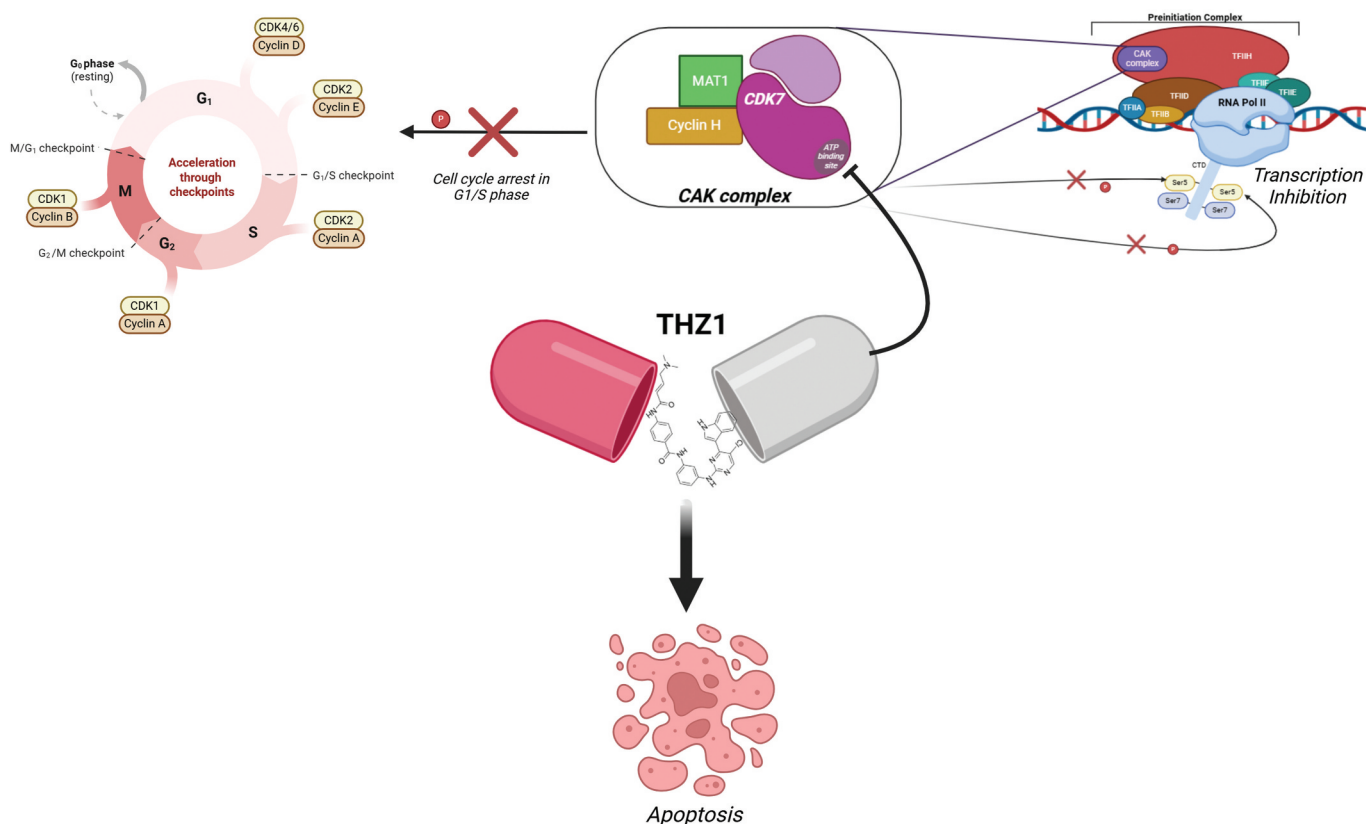


Figure 3. Mechanism of action of THZ1: THZ1 selectively inhibits CDK7, resulting in the prevention of serine 5 phosphorylation on RNAPII, thereby disrupting transcriptional elongation. Furthermore, THZ1 impedes the phosphorylation of cyclins, leading to cell cycle arrest at the G1/S transition and consequently inhibiting cellular proliferation. Created in BioRender. Rocco, M. (2025) <https://BioRender.com/qoqo8xj>.

that CDK7 inhibition impairs PIC stability and reduces global gene expression. However, the exact mechanism by which CDK7 regulates transcription remains unclear and may depend not only on phosphorylation of the CTD but also on its interaction with other transcription factors such as TFIIE and Spt5 [28]. Of note, CDK7 knockout cell lines have shown only a partial reduction in RNAPII phosphorylation [33]. Moreover, altered regulation of CDK7 may promote tumor growth by increasing the expression of oncogenes, enhancing cell survival, regulating cellular metabolism by influencing metabolic enzymes such as GLUT1 and LDHA, as illustrated in Figure 1 [2,28,35].

2.2. CDK7 inhibitors

CDK7 has been widely investigated as a therapeutic target for cancer treatment due to its involvement in controlling aberrant cell cycle progression and transcription in tumor cells [36], for this reason, the use of CDK7 inhibitors is becoming an increasingly promising option in the treatment of patients with cancer. Several CDK7 inhibitors with different chemical structures have been developed and tested in the preclinical setting (Figure 2, Table 1)

The most extensively studied inhibitor is THZ1, which inhibits CDK7 by binding to an allosteric site, achieving greater specificity and reducing off-target effects. It forms a covalent bond with Cys312, located outside the ATP-

binding site, through its acrylamide moiety, which significantly contributes to its activity [37] (Figure 3). However, the effects of some inhibitors, including THZ1, are attributable not only to the inhibition of CDK7 but also to the inhibition of other CDKs [38]. For this reason, one of the main limitations of THZ1 is its poor selectivity, as it binds covalently not only to CDK7 but also to CDK12 and CDK13 (to Cys1039 and Cys1017, respectively), inhibiting their activity [31]. This broad inhibition can affect the expression of a wide range of genes, including those involved in immune responses and cell survival, potentially leading to adverse effects. The lack of specificity of THZ1 requires careful evaluation in its clinical application. Although it may exhibit potent antitumor activity, the risks associated with off-target effects and toxicity may limit its therapeutic index [37]. To overcome this issue, more selective inhibitors, such as YKL-5-124 and YPN-005, have been developed. YPN-005 demonstrated greater antitumor activity than THZ1 by inhibiting phosphorylation of RNAPII, resulting in cell cycle arrest, induction of apoptosis, and reduced ASCL1 expression [39]. These results were confirmed in mouse models, where the treatment exhibited limited side effects [40]. Thus, it appears that this inhibitor may offer a better therapeutic profile than THZ1, owing to fewer off-target effects on CDK12 and CDK13. Instead, YKL-5-124 is a selective, irreversible, and covalent inhibitor of CDK7. This inhibitor causes an aberrant progression of the cell cycle, resulting in

a slowdown rather than an interruption, and does not induce apoptosis [41]. Treatment with YKL-5-124 has been shown to increase genomic instability in SCLC cells, leading to the accumulation of DNA damage. Additionally, CDK7 inhibition by YKL-5-124 enhanced the efficacy of PD-L1 inhibitors [42]. Another inhibitor that is gaining attention is LDC4297, which non-covalently blocks ATP binding to CDK7, thereby preventing its catalytic activity. This leads to a reduction in the phosphorylation of the CDK T-loop and a decrease in global transcriptional activity, highlighting the key role of CDK7 in transcription regulation and cell cycle control. LDC4297 allows for the study of cellular dependency on CDK7 and enables comparisons with other inhibitors, such as THZ1, which instead acts covalently [43].

Other CDK7 inhibitors include Triptolide and SNS-032, which have already been reviewed by Moser et al., who demonstrated that their inhibition of the TFIIH complex in KRAS/TP53 mutant PDAC leads to RPB1 degradation and caspase-8-dependent apoptosis [44].

2.2.1. Effects of CDK7 inhibition on cell cycle

CDK7 is a universal CAK that plays a crucial role in activating all cyclin-dependent kinases (CDKs) involved in the cell cycle, including CDK4, CDK6, CDK1, and CDK2. By activating these CDKs, CDK7 facilitates their progression through the various stages of the cell cycle. Additionally, CDK7 regulates the timing of cyclin expression, ensuring proper cell cycle progression [25]. In particular, although each CDK may have distinct activation mechanisms, CDK7 is essential for T-loop phosphorylation and the stabilization of CDK-cyclin complexes. These functions are critical for the precise temporal and spatial regulation of cell division [45]. As a result, deletion of CDK7 by CRISPR-Cas9 promoted apoptosis and suppressed the cell cycle [32]. In addition, the use of LDC4297 caused cell cycle arrest in G1 and population reduction in S phase in MIA PaCa-2 and PANC-89, MIA PaCa-2 cells exhibited significant changes only at higher LDC4297 concentrations. Lastly, the synergistic interaction between the CDK4/6 inhibitor palbociclib and LDC4297 increased the G1 subpopulation in both MIA PaCa-2 and PANC-89 cells [43].

2.2.2. Effect of CDK7 inhibitors on transcription

CDK7 is involved in several steps of transcription. During the initiation phase, as part of the TFIIH complex, it phosphorylates the Ser5 residue in the CTD of RNAPII, facilitating the transition from initiation to elongation of transcription [2,28]. CDK7 also regulates other transcription factors involved in assembling the PIC through a process known as promoter escape [31]. Of note, given its dual role in transcription and cell cycle progression, the inhibition of CDK7 by selective inhibitors is expected to block both processes. This dual inhibition, however, raises concerns about toxicity: although blocking CDK7 stops cancer cell proliferation, it can also cause diffuse transcription alteration in non-cancerous cells [46]. A study conducted on mutant/mutant (mut/mut) mouse embryonic fibroblasts (MEFs) deprived of CDK7 demonstrated that the absence of CDK7 does not affect the phosphorylation of the Ser5 residue on RNAPII. This finding suggests that other kinases can compensate for the loss of CDK7 in

phosphorylating Ser5, indicating that CDK7 is not essential for the initiation of transcription, and other kinases perform this role [30]. Further studies on NSCLC cell lines (A549 and H1975) have shown that treatment with CDK7 inhibitors, including LDC4297, significantly reduces nascent RNA transcription and RNAPol levels. However, transcription is not completely halted, suggesting that while CDK7 plays an important role, it is not essential for transcription [28]. The hypothesis that CDK7 may not be essential for transcription is supported by other studies using highly selective CDK7 inhibitors, such as YKL-5-124, which is even more specific than THZ1. For example, treatment with YKL-5-124 slowed but did not reduce RNAPII phosphorylation, unlike THZ1. However, combining YKL-5-124 with a CDK12/13 inhibitor reproduced the effects observed with THZ1 [37].

2.2.3. Effects of CDK7 inhibition on molecular immunity

CDK7, as a bifunctional hub of TFIIH kinase and CAK, is central to transcriptional and immune regulation, and is regarded as a key gene linking these two processes. Once its activity is inhibited, RNAPII in the promoter region, causes a rapid decrease in global transcriptional levels, which in turn broadly affects a number of key immune pathways, including antigen presentation, interferon response, chemokine release, and expression of immune checkpoint molecules [42,47]. Super-enhancer (SE)-dependent transcriptional processes are particularly sensitive to CDK7 inhibition. This type of inhibition leads to a 'downgrade' of the MYC-overexpressing transcriptional network and downregulates PD-L1 expression through the MYC-PD-L1 signaling axis, alleviating immunosuppression at the molecular level and providing a mechanistic basis for understanding its synergistic effect with PD-1/PD-L1 blockade therapy [4,46]. In addition, selective inhibition of CDK7 induces replication stress and micronucleus formation, which in turn activates natural immune-related signals such as TNF, CXCL9/10, and interferon, contributing to the transition of immunologically 'cold' tumors to an inflammatory and immune-activated state, and creating the molecular conditions necessary for the potentiation of immune checkpoint inhibitors (ICIs) [42]. In NSCLC, the CDK7 inhibitor THZ1 reduces PD-L1 expression through the p38 α -MYC-PD-L1 signaling cascade and shows synergistic effects with anti-PD-1 therapy at both molecular and functional levels [4]. In SCLC, the highly selective inhibitor YKL-5-124 inhibits replication-associated transcription, induces genomic instability, and upregulates the TNF/CXCL9/10/IFN signaling pathway, thereby activating the anti-tumor immune response [42]. In PDAC, THZ1 significantly interferes with the phenomenon of 'transcription addiction' through selective inhibition of CDK7, which preferentially inhibits cell cycle progression and NF- κ B-related transcriptional programs, and thus reduces immunosuppression-related genes [48]. In addition, the co-delivery of BRD4 and CDK7 inhibitors by nano-carriers has been demonstrated to synergistically inhibit super-enhancer-driven oncogenic and immunosuppressive transcriptional networks. This strategy enhances the anti-tumor effect while mitigating systemic toxicity, which provides theoretical and experimental support for combining it with ICIs, STING agonists or radiotherapy [49].

2.2.4. Effects of CDK7 inhibition on cellular immunity

At the cellular level, CDK7 inhibition can remodel the tumor immune microenvironment (TME). On one hand, it enhances the immunogenicity of tumor cells and improve their ability to be recognized by the immune system; on the other hand, it can regulate the composition, spatial distribution, and functional status of the immune cells, so as to transform the tumor into immune-deserting tumors into inflammatory-infiltrating phenotypes [4,42,50]. Several experimental models of solid tumors have shown that CDK7 inhibition promotes infiltration of effector T cells and enhances their function. For example, in SCLC, YKL-5-124 induced genomic instability and endogenous immune activation signals to enhance tumor immunoreactivity; combined with PD-1 blockade, it further increased the infiltration and killing activity of CD8⁺ T cells, resulting in more sustained tumor suppression and concomitant T-cell migration from the periphery to the core of the tumor [42]. In NSCLC, either pharmacological inhibition (e.g., THZ1) or knockdown of CDK7 enhances CD8⁺ T cell infiltration and synergizes with anti-PD-1 therapy. This synergistic effect was attenuated if CD8⁺ T cells were removed, suggesting that the infiltration and maintenance of effector T cells play a decisive role in this process and are far from being a change at the level of molecular pathways alone [4]. In addition, CDK7 inhibition may also affect the inflammatory program of myeloid cells such as macrophages, which may contribute to the alleviation of pathologic inflammation or the treatment of related inflammatory responses. However, there is a potential risk that excessive suppression of innate immune functions, including antigen presentation, chemokine secretion, and recruitment of immune cells, may have adverse effects [51]. CDK7 inhibition also systematically regulates the cellular composition and spatial architecture of the TME. For example, when combined with CDK4/6 inhibitors, it elevates the proportions of CD8⁺ T cells, CD4⁺ T cells, B cells, and NK cells in the TME, while reducing ICIs immunosuppressive myeloid cells (e.g., certain macrophage subsets). Furthermore, spatially, it induces the otherwise confined to the tumor borders of CD8⁺ T cells to migrate toward the tumor interior, optimizing the immune landscape [50].

3. CDK7 in lung cancer

In the context of lung cancer, CDK7 plays a crucial role due to its involvement in both the cell cycle and transcription by regulating RNAPII. Studies in NSCLC have shown that high CDK7 expression is associated with poor prognosis and increased tumor aggressiveness, suggesting that its activity contributes to tumorigenic processes such as uncontrolled proliferation and altered metabolism of cancer cells [3]. Kuempers et al. evaluated CDK7 protein expression in a large cohort of patients with LUAD and LUSC, correlating CDK7 levels with clinical-pathological data. In adenocarcinoma patients, high CDK7 levels were associated with reduced disease-free survival (DFS) and overall survival (OS). A similar trend was also observed in patients with LUSC, although the results were not fully consistent, likely due to the small size of the cohort analyzed [3]. Additionally, Wang et al. suggested

that CDK7 may influence pathways such as p38 α /MYC/PD-L1 signaling, which could be related to mechanisms of drug resistance and metastatic capacity. These findings were supported by experiments conducted in murine models [4].

3.1. CDK7 inhibition in SCLC

Currently, SCLC remains a therapeutic challenge due to its aggressiveness and resistance to conventional treatments. SCLC is one of the few cancers in which mutations in the *RB* and *p53* regulators of transcription are the primary genetic cause. The most frequent somatic alterations involve transcription factors or chromatin modifiers, such as *MYC*, *SOX2*, *MLL1/2*, *RBL2*, and *p53* [52]. In this challenging context, inhibition of factors involved in gene transcription, such as CDK7, has shown promising results [42]. THZ1, one of the first covalent competitive ATP inhibitors, was studied for its ability to covalently bind Cysteine 312 (Cys312) at the C-terminal site outside the ATP binding site [31,37] as shown in Figure 3. Preclinical studies demonstrated that SCLC cells are highly sensitive to the perturbation of the transcriptional state induced by CDK7 inhibition. The efficacy of THZ1 was further confirmed in RP GEM mouse models, which harbor conditional knockouts of the *p53* and *RB* genes in the lung, promoting SCLC development. Treatment resulted in the downregulation of *ASCL1*, impairing transcription of enhancers critical for maintaining neuroendocrine identity and cell proliferation. Notably, THZ1 treatment exhibited lower toxicity compared to conventional chemotherapy, suggesting its potential as a promising therapeutic strategy for SCLC [39]. However, the possibility of developing resistance mechanisms or off-target effects has not been extensively explored, representing a critical limitation for clinical translation. In parallel, Zhang et al. studied YKL-5-124, a selective reversible inhibitor of CDK7 [42]. This compound disrupts cell cycle progression by inducing DNA replicative stress and genome instability in tumor cells, leading to a cellular response characterized by the release of multiple pro-inflammatory cytokines and chemokines. This suggests a potential interaction between CDK7 inhibition and the immune microenvironment. In mouse models, YKL-5-124 was also tested in combination with a PD-1 inhibitor, resulting in strong antitumor immunity and a survival benefit. These findings suggest that this more specific inhibitor may slow cell cycle progression by enhancing the immune response in SCLC, thus supporting the development of novel protocols combining CDK7 inhibitors with immunotherapy [42]. Combination strategies are a key approach for cancer treatment, as they enhance therapeutic efficacy. Remarkably, the combination of THZ1, which inhibits transcription, and topotecan, which inhibits topoisomerase I, targets tumor vulnerabilities on multiple fronts [53]. Sun et al. demonstrated that THZ1 sensitizes SCLC cell lines to topotecan by exacerbating DNA damage. THZ1 inhibits transcription by preventing RNAPII phosphorylation, while topotecan acts by inhibiting topoisomerase I, leading to the accumulation of topoisomerase I-DNA covalent complexes and single-strand breaks. The reduced transcription impairs the cell's ability to respond to

DNA damage efficiently, leading to the accumulation of DNA damage, cell cycle arrest, and apoptosis [53]. This combination strategy highlights the potential for targeted therapies that exploit the synergy between transcription inhibitors and DNA-damaging agents, making treatment more effective against SCLC. However, it remains to be seen whether these synergistic effects will translate into lasting clinical responses, especially considering the well-documented ability of SCLC to rapidly develop resistance under therapeutic pressure.

3.2. CDK7 inhibition in NSCLC

CDK7 has been identified as a potential prognostic biomarker in NSCLC, significantly impacting tumor progression through its roles in transcription and the cell cycle [3]. Another important aspect is its influence on resistance to therapies, particularly in the context of targeted treatments. For example, Ji et al. explored the efficacy of THZ1 in overcoming resistance associated with EMT using A549 and H1975 NSCLC cell lines. These models were employed to test how CDK7 inhibition could affect resistance mechanisms to third-generation EGFR-TKIs. While a direct link between CDK7 and resistance to EGFR-TKIs was not established, the study found that CDK7 inhibition reduced the expression of EMT markers, suggesting that CDK7 may influence cancer cells' ability to adapt to therapies, potentially restoring sensitivity to these treatments [54]. Furthermore, CDK7's impact on SOX2, a transcription factor crucial for maintaining neuroendocrine cell identity and resistance in squamous forms of NSCLC, has been explored. The efficacy of THZ1 was investigated on three SOX2-amplified lung SCC-derived cell lines (H520, H1703 and HCC95) and two SOX2 non-amplified lung SCC-derived cell lines (SK-MES-1 and H226). Treatment with THZ1 suppressed tumor growth and decreased transcriptional activity specifically in cells with SOX2 amplification [55]. In addition to its role in transcription and cell cycle regulation, CDK7 inhibition appears to influence cellular metabolism, a key factor in sustaining the high energy demands of cancer cells [2,35]. One study showed that CDK7 promotes glucose uptake and utilization, thereby increasing the energy consumption of A549, H460 and HCC827 NSCLC cells. This was associated with enhanced expression of genes involved in glucose uptake and metabolism, creating a metabolic environment conducive to tumor growth. Conversely, inhibition of CDK7 by THZ1 led to a decrease in GLUT1 mRNA and protein levels, as well as reduced glucose transport [35]. Similarly, another study revealed that THZ1-mediated inhibition of CDK7 resulted in reduced glucose uptake, which consequently led to decreased ATP production and impaired biosynthesis of essential biomolecules in H1299, A549, H292 and H23 NSCLC cells. This reduced the ability of cancer cells to sustain rapid proliferation. Specifically, THZ1 inhibited key steps of glycolysis without affecting glutamine metabolism, leading to decreased glucose uptake and lactate secretion [2]. Although these results suggest a direct link between CDK7 activity and metabolic control, they remain limited to in vitro models. Considering the known metabolic plasticity of NSCLC, future work will need to assess whether

tumors can overcome CDK7 inhibition by reorganizing their metabolism toward alternative nutrient sources.

Of note, this dual action not only limits tumor growth but may also reduce the ability of cells to develop resistance mechanisms, a phenomenon often associated with metabolic plasticity [56]. In addition, CDK7 inhibition affects specific NSCLC subpopulations and immune responses. For instance, one subgroup of lung adenocarcinomas is driven by the *EML4-ALK* translocation. Although initial responses to inhibitors are promising, acquired resistance is a clinically significant issue [57]. Paliouras et al. studied the effects of CDK7 inhibition by THZ1 on lung carcinoma cells with acquired resistance to crizotinib, ceritinib, and alectinib, derived from parental H3122 cells and STE-1 cells. Remarkably, this treatment reduced transcription of pro-survival genes and dramatically decreased *MYC* levels, resulting in a potent antiproliferative effect. Furthermore, combining THZ1 with an ALK inhibitor showed a promising synergistic effect, sensitizing cells and helping overcome acquired resistance [57]. The use of combination strategies was also explored by Wang et al., who demonstrated that THZ1 potentiates the efficacy of anti-PD-1 immunotherapy in NSCLC cells. In particular, CDK7 inhibition promoted the recruitment of infiltrating CD8+ T lymphocytes, reduced PD-L1 expression, and further lowered *MYC* levels, thereby enhancing the antitumor immune response. While these results point to an immunomodulatory role for CDK7 inhibition, the complexity of the TME in patients may attenuate such effects, underscoring the need for validation in clinical trials. These findings highlight how combining THZ1 with targeted therapies or immunotherapies may offer an effective strategy to overcome resistance in lung cancers [4].

Finally, in the study by Ji et al., LDC4297, a potent CDK7 inhibitor, was evaluated in NSCLC models using the A549 and H1975 cell lines. Treatment with LDC4297 significantly reduced cell proliferation, induced cell cycle arrest, and promoted apoptosis. These findings highlight the potential therapeutic efficacy of CDK7 inhibition in NSCLC and suggest the importance of further testing additional CDK7 inhibitors in lung cancer models [28]. However, without data from clinical settings, it remains uncertain whether the preclinical potency of CDK7 inhibitors will translate into meaningful therapeutic benefits for patients. Therefore, although the preclinical rationale is sound, clinical validation is the necessary next step before CDK7 inhibition can realistically be positioned as a therapeutic strategy in NSCLC.

4. CDK7 inhibition in PDAC

Recent preclinical studies showed that PDAC is relatively sensitive to drugs targeting transcription and particularly the CDK7 inhibitor THZ1. Thus, the development of CDK7 inhibitors is becoming a promising choice in this field of oncology. Most studies focused on THZ1, a nonselective covalent inhibitor, which also inhibits CDK12 and CDK13, which are both expressed in PDAC cells [58]. Numerous studies in recent years have utilized in vitro and in vivo models to demonstrate the efficacy of CDK7 inhibition. These studies employed different cell lines, some of which were more sensitive to CDK7

inhibition than others. Specifically, the BxPC-3, MIA PaCa-2, and AsPC-1 cell lines exhibited the highest sensitivity, while the PANC-1 and SW1190 cell lines were less responsive. The sensitive cell lines showed a decrease in RNAPII phosphorylation upon treatment [48]. Of note, the most frequent mutation in PDAC is in the *KRAS* gene, which is mutated in more than 90% of cases. Particularly common are the G12D and G12V mutations, which are critical for tumor development. The G12D mutation is observed in 45% of cases [54] while the G12V mutation occurs in 32% of cases [59], and plays a significant role in driving tumorigenesis [60]. Studies on *KRAS*-mutant cell lines have shown that those with the G12V mutation (e.g., CAPAN-2 and PANC03.27) are more sensitive to treatment with THZ1 compared to cell lines harboring the G12D mutation (e.g., SW1990, PANC02.03, and PANC10.05) [33]. *KRAS*-mutant tumor cells often exhibit resistance to conventional treatments, leading to exploration of TNF-related apoptosis-inducing ligand (TRAIL) agonists as a potential therapeutic strategy. Interestingly, *KRAS* mutations have been found to increase cell susceptibility to THZ1.

Several findings suggest that the *KRAS* mutational subtype plays an important role in determining sensitivity to CDK7 inhibition and the efficacy of THZ1. In vitro, THZ1 showed greater pro-apoptotic effects and lower IC50 values in PDAC cell lines with *KRAS*-G12V compared to *KRAS*-G12D. Clinically, patients with *KRAS*-G12D had significantly shorter overall and disease-free survival than those with *KRAS*-G12V, and low CDK7 expression was associated with improved DFS only in the G12V subgroup. These results indicate that *KRAS* subtype could serve as a biomarker for patient stratification in CDK7-targeted therapies. However, additional factors may contribute to treatment sensitivity and should be further investigated [33].

Furthermore, CDK7 inhibition has been shown to downregulate key anti-apoptotic regulators such as CFLAR, MCL1, and XIAP, thereby enhancing the apoptotic response in *KRAS*-mutant PDAC. In this context, combination therapies using TRAIL and TFIH inhibitors have demonstrated a synergistic effect, even in models harboring *KRAS* and TP53 mutations [44].

While *KRAS* mutational status may influence the differential response to THZ1 in PDAC cell lines, additional molecular determinants – such as those involved in apoptotic regulation – are likely to contribute to sensitivity. Therefore, further mechanistic studies, as well as clinical investigations, are warranted to identify reliable biomarkers and develop effective patient stratification strategies.

In addition to THZ1, triptolide was also tested in *KRAS* mutant cells. Triptolide downregulates the expression of transcription factors like STAT3 and FOSL1 in *KRAS* mutant signaling and acts on TFIH, enhancing the effect of TRAIL. Thus, the combination of THZ1 and triptolide could offer new therapeutic opportunities for treating *KRAS*-mutant PDAC [44].

A water-soluble analog of triptolide, Minnelide, was synthesized and tested in MIA PaCa-2 and PANC-1 cell lines, and in a murine model with athymic mice (4–6 weeks old) where cancer cells are injected into the pancreas using Matrigel for implantation. Additionally, a SCID mouse model was used, in which human pancreatic tumors are implanted subcutaneously [61].

Based on these studies, a phase I study (NCT03117920) is currently ongoing for Minnelide. Combining TRAIL inhibitors with TFIH inhibitors may also enhance cell death in *KRAS*-mutant tumors, offering new potential therapeutic avenues for PDAC treatment [44].

Further studies have been performed with the inhibitor LDC4297, which contains a pyrazole[1,5-*a*][1,3,5]triazine core. This highly specific inhibitor non-covalently blocks ATP binding to CDK7. Treatment with LDC4297 reduced cell viability in several cell lines (PANC-89, PT45, BxPc3), while sensitivity was intermediate in MIA PaCa-2 cells and lower in other lines, including PANC-1, CAPAN-1, CAPAN-2, AsPC1, and A8184 [43]. Several studies have been conducted showing that the use of THZ1 in vitro and in vivo reduces tumor volume and cell proliferation by increasing apoptosis and decreasing the transcription of the antiapoptotic genes *MCL1*, *BIRC3* and *XIAP* [44,52]. In particular, THZ1 inhibited cancer cell growth, and promoted apoptosis by inhibiting BCL2 and MCL1 while suppressing the cell cycle in PANC-1, AsPC-1, BxPC-3, MIA PaCa-2, SUIT-2, TKCC-10 [32]. The activity of THZ1 has also been demonstrated in PDAC tumors in mice originating from CAPAN-2 cells harboring the *KRAS*-G12V mutation, in a dose-dependent manner. THZ1 hindered tumor growth in a dose-dependent manner in mice [33]. The use of CDK7 inhibitors, such as triptolide or THZ1, led to the subsequent inhibition of the TFIH complex, an essential factor for transcription. A main result was the downregulation of RNAPII subunit RPB1 and CASP8 and FADD-like apoptosis regulator (CFLAR) proteins in a concentration-dependent manner [44]. Interestingly, to understand if the binding of CDK7 to THZ1 was necessary to cause apoptosis, experiments were conducted separately using a modified version of THZ1 (THZ1-R) and a mutant form of CDK7 (C312S), neither form allowing the binding of CDK7 to THZ1. The results showed that neither compound caused cell death, blocking activation of Caspase-3 and suppression of *MYC* [58]. This is in agreement with another study showing that inhibition of CDK7 led to reduced expression of c-MYC [62] because CDK7 was required for the transcriptional activation of c-MYC through the phosphorylation of RNAPol in PANC-89 and MIA PaCa-2 [43]. Of note, c-MYC seems to play a crucial role in treatment response. In some cell lines that were not sensitive to THZ1, *MYC* expression is very low, while in cell lines that develop resistance to the drug, *MYC* expression was elevated, suggesting that c-MYC may contribute to resistance to THZ1 [48]. In addition, CDK7 plays a crucial role in the activation of the STAT3-MCL1-CHK1 pathway, which is important for cell survival and response to chemotherapy. The use of CDK7 knockout cell lines showed significant reduction of STAT3 phosphorylation, which was more pronounced in the presence of gemcitabine and paclitaxel chemotherapy treatments. Furthermore, protein levels of MCL1 were markedly decreased, as were those of CHK1, an MCL1-regulated target involved in cell cycle control and DNA damage repair. The reduction of CHK1 was particularly significant after 24 hours of treatment in TB32047 and MIA PaCa-2 cells [32].

4.1. Effect of combinations with CDK7 inhibitors in PDAC

It has been observed that the combination of CDK7 inhibitors with chemotherapeutics or CDK4/6 inhibitors (e.g., palbociclib) can yield enhanced therapeutic outcomes. As highlighted in the study by Zeng et al., the combined treatment of THZ1 with chemotherapeutics (gemcitabine and paclitaxel) significantly reduced tumor volume, weight, and size in an orthotopic mouse model, where TB32047 tumor cells were orthotopically injected into the tail of the pancreas of female C57BL/6JRj mice via laparotomy, compared to the individual treatments. Additionally, the combination treatment increased the apoptosis rate and enhanced caspase 3/7 activity [32]. Of note, the combination of palbociclib and LDC4297 led to an increase in the cell population in the G1 phase, with a reduction in the S and G2/M phases. This is likely due to the inhibition of ATP binding and limited T-loop phosphorylation. However, the combined treatment reduced proliferation only at low concentrations of LDC4297; above a certain threshold, the effect of palbociclib was minimal. In particular, the threshold concentration varied by cell line, with a lower threshold for PANC-89 compared to MIA PaCa-2 [43]. A similar result was observed using the inhibitor SNS-032, which led to decreased phosphorylation of RNAPII and T-loop of other cyclin-dependent kinases, thereby inhibiting transcription and cell cycle progression. SNS-032 in combination with TRAIL also showed enhanced treatment efficacy by inducing a higher rate of cell death in PANC-VH1 [44].

5. Resistance to CDK7 inhibitors

CDK7 inhibitors, such as THZ1, have been shown to significantly inhibit CDK7. However, despite the promising results demonstrated by THZ1 and other inhibitors in preclinical studies, resistance to these molecules is expected to emerge during clinical trials. Therefore, it is crucial to identify potential mechanisms of resistance early on and develop strategies to overcome this phenomenon [57,58]. A study aimed at identifying molecular changes associated with resistance to THZ1 generated cellular models of resistance. No acquired mutations in binding targets or changes in CDK7 transcript levels were observed. However, when studying ATP-binding cassette (ABC) family transporters, it was found that THZ1-resistant cells exhibited high levels of ABCB1 and ABCG2, which contributed to increased drug efflux, thereby reducing intracellular efficacy [63]. Sava et al. identified the same resistance mechanism in response not only to THZ1 but also to the reversible inhibitor ICEC0942. However, the efficacy of these inhibitors varied according to the expression levels of ABCB1 and ABCG2 in different cell lines, suggesting that the expression of ABC transporters could serve as a predictive biomarker for response to CDK7 inhibitors [64]. Of note, we recently observed the critical role of ABCB1 in resistance to paclitaxel in PDAC cell lines (PANC-1, SUI-02, and PATU-T), suggesting that combinations with additional kinase inhibitors could be further (pre)clinically explored as therapeutic strategies to overcome this resistance in PDAC [65]. In conclusion, further investigation into the mechanisms driving resistance to CDK7 inhibitors is essential. Current

evidence suggests that combining CDK7 inhibitors with modulators of ABC transporters may enhance therapeutic responses and help prevent the development of resistance [63].

6. Conclusion

In recent years, CDK7 has emerged as a promising target in cancer molecular biology, as it regulates key processes in tumor cells such as cell cycle, transcription and metabolism. Its role in carcinogenesis and therapy resistance has been investigated in various tumor types, including SCLC, NSCLC, and PDAC. In preclinical models of these malignancies, CDK7 inhibition has demonstrated significant effects in reducing cell proliferation, although with varying sensitivity levels depending on the tumor model type and mutational profile [38,41,66].

It has been demonstrated that CDK7's function in transcriptional regulation and cell cycle control is crucial. THZ1, the most extensively studied CDK7 inhibitor in these tumors, is a nonselective covalent inhibitor that binds to the allosteric site of CDK7. In multiple studies, THZ1 has led to a reduction in cell proliferation, promotion of apoptosis, and alteration of transcription factor expression [39]. Specifically, THZ1 inhibits RNAPII phosphorylation, thereby preventing the transcription of genes essential for tumor survival and progression. This effect has been observed in all tumors analyzed in this review, suggesting a shared mechanism that could be exploited across different cancer types. In SCLC, THZ1 has contributed to reduced proliferation and enhanced apoptosis, particularly in the most sensitive cell lines (H69AR and NCI-H466), as well as to the downregulation of crucial neuroendocrine factors such as ASCL1 [10]. A similar effect has been observed in NSCLC, where CDK7 inhibition has been shown to reduce EMT and improve response to EGFR-TKI treatment, indicating a potential role of CDK7 in resistance mechanisms. In PDAC, THZ1 has demonstrated comparable effects, depending on the specific cell line used. The primary outcomes include reduced STAT3 phosphorylation, improved chemotherapy efficacy, particularly in combination with gemcitabine and paclitaxel, as well as inhibition of cell proliferation, and promotion of apoptosis through the downregulation of BCL2 and MCL1 [32]. Another promising inhibitor tested in vitro, LDC4297 has shown efficacy in various PDAC cell lines such as BxPc3 and PANC-89 [32].

Preclinical studies suggest that advances in CDK7 inhibitor research hold the potential to enhance the therapeutic management of NSCLC, SCLC, and PDAC, particularly in patients with primary or acquired chemotherapy resistance. If clinically validated, these inhibitors could inhibit tumor cell proliferation and promote apoptosis, thereby improving the efficacy of combination therapies. However, further research, clinical trials, and the identification of predictive biomarkers are crucial for enabling personalized treatment approaches. Moreover, despite promising preclinical results, challenges remain with CDK7 inhibitors, including issues with specificity and resistance. It is important to critically consider the limitations associated with CDK7 inhibitors, including their incomplete specificity, potential off-target effects (e.g., inhibition of CDK12/13), and the risk of toxicity due to

partial arrest of global transcription. In the future, it will be essential to focus on developing more selective inhibitors, optimizing dosing regimens, and identifying predictive biomarkers to maximize efficacy while minimizing toxicity. Additionally, while combination strategies with chemotherapy or targeted therapies seem to improve therapeutic outcomes, further studies are needed to determine the most effective strategies to optimize benefits. Therefore, continued advanced preclinical investigations are essential to clarify the role of CDK7 as a therapeutic target and to fully assess the potential of these inhibitors in treating SCLC, NSCLC, and PDAC in the clinical setting.

7. Expert opinion

Advancements in CDK7 inhibitor research hold the potential to significantly impact the treatment of currently challenging malignancies such as NSCLC, SCLC, and PDAC, particularly in patients who develop resistance to conventional therapies like chemotherapy. If the promising results observed in preclinical models are confirmed in clinical settings, these inhibitors could provide novel therapeutic options capable of reducing tumor cell proliferation and enhancing apoptosis when combined with other treatment modalities. This combination approach could improve overall treatment efficacy while reducing reliance on second-line therapies [32,40,42]. However, before these inhibitors can be integrated into clinical practice, extensive testing, large-scale validations, and rigorous clinical trials are required [36]. Additionally, the development of predictive biomarkers will be crucial for identifying patients most likely to benefit from these therapies, allowing for more personalized treatment strategies tailored to the tumor's molecular profile [36,67]. Despite promising preclinical evidence, the use of CDK7 inhibitors is not without limitations, such as the lack of specificity of some inhibitors, which also target other kinases beyond CDK7, including CDK12 and CDK13 [64].

This polypharmacology (i.e. multi-target activity) may contribute to the remarkable antitumor efficacy observed with THZ1, but it also raises concerns about potential toxicity. Inhibition of CDK12/13 may impair the expression of DNA damage response genes and other transcripts essential in normal cells, which may narrow the therapeutic window and cause systemic side effects [46,68].

The search for therapeutic solutions in lung and pancreatic tumors is particularly complex, as patients with these malignancies frequently develop chemoresistance, and the lack of predictive molecular biomarkers in PDAC and SCLC makes treatment personalization challenging. In this review, we examined the *in vitro* and *in vivo* use of CDK7 inhibitors, with results that, while promising, require confirmation through additional preclinical studies and future clinical trials to better define their therapeutic role. An innovative approach currently being explored is the use of CDK7 inhibitors in combination with other therapies. For instance, in a pancreatic cancer mouse model, where TB32047 tumor cells were orthotopically injected into the pancreas of female C57BL/6JRj mice via laparotomy, the combination of THZ1 with gemcitabine has shown synergistic effects [32].

Similarly, the use of THZ1 with EGFR inhibitors demonstrated increased antitumor efficacy in NSCLC models [54]. Additionally, in PANC-89 and MIA PaCa-2 cell lines, CDK7 inhibition has led to the downregulation of MYC, a key factor in tumor proliferation and survival [43]. In THZ1-resistant cell lines, such as BxPc3 and SUIT-2 [58] and NSCLC models [4] expression remained high, suggesting that MYC might mediate resistance to treatment. Therefore, the combined inhibition of CDK7 and MYC could be an effective strategy to enhance therapeutic response [4,43].

An intriguing aspect is the modulation of the immune response by CDK7 inhibition, as reported in several studies [4,42]. In NSCLC, CDK7 inhibition led to CD8⁺ T lymphocyte infiltration and a reduction in PD-L1 expression. When combined with immunotherapy, THZ1 improved the antitumor response [4], a finding that should also be explored in PDAC, where resistance to immunotherapy remains a challenge. Another fundamental aspect that requires further investigation is the selectivity of these drugs. As mentioned earlier, inhibitors such as THZ1, although promising, also inhibit other CDKs, including CDK12 and CDK13. Careful consideration of this off-target activity will be crucial in clinical translation, as excessive suppression of global transcription could cause dose-limiting toxicities. The development of more selective inhibitors, such as LDC4297 and YKL-5-124, is already in progress, although they have demonstrated lower efficacy [37,43]. This raises the question of whether polypharmacology should be considered a limitation or an opportunity to maximize therapeutic efficacy. In fact, some studies suggest that the impressive efficacy of THZ1 may be partly attributable to its inhibition of CDK12/13 as well as CDK7, thereby enhancing global transcriptional repression [37,68]. To overcome this limitation, it will be essential to characterize the molecular profile of tumors to further personalize treatment. In particular, research is progressing toward a deeper understanding of resistance mechanisms and oncogenic pathways, such as those mediated by c-MYC and KRAS, which will enable the development of combination strategies involving CDK7 inhibitors and other targeted or immunotherapeutic approaches [21,43,50,52]. This could pave the way for innovative and efficient therapeutic strategies, even for the most aggressive and resistant tumors. However, the variability in response among different cell lines with distinct molecular characteristics, such as *KRAS* mutations in various PDAC models suggests that some tumors may be intrinsically resistant, necessitating a personalized approach and highlighting potential limitations due to tumor molecular heterogeneity [33,44]. The most effective strategy is likely to be an integrated approach that combines multiple therapeutic targets. In summary, if the current relevance of CDK7 is confirmed, the next 5–10 years may witness the evolution of clinical studies incorporating CDK7 inhibition as a therapeutic component. However, while CDK7 inhibitor research is rapidly evolving and holds the potential to transform the therapeutic landscape, clinical application requires further studies to improve selectivity, reduce side effects, and define optimal combinatory strategies. Only through an integrated and

multidisciplinary approach will it be possible to translate research into clinical practice, ultimately leading to tangible benefits for patients.

Abbreviations

ABCB1	Adenosine triphosphate binding cassette subfamily B member 1
ABCG2	Adenosine triphosphate binding cassette subfamily G member 2
ALK	Anaplastic lymphoma kinase
ASCL1	Achaete-scute complex-like 1
ATP	Adenosine triphosphate
BIRC3	Baculoviral IAP repeat-containing 3
BRAF	B-Raf proto-oncogene
BRCA1	Breast cancer 1
BRCA2	Breast cancer 2
CAK	Cyclin-dependent activating kinase
CDK	Cyclin-dependent kinases
CFLAR	Cellular Fas-associated death domain-like interleukin-1-converting enzyme
CTD	Carboxy-terminal domain
DYRK	Dual-specificity tyrosine-phosphorylation-regulated kinase
EGFR	Epidermal growth factor receptor
EML4	EML4-ALK fusion gene
EMT	Epithelial-mesenchymal transition
GLUT1	Glucose transporter 1
GEM	Gemcitabine
GSK3b	Glycogen synthase kinase 3 beta
HER2	Human epidermal growth factor receptor 2
HNSCC	Head and neck squamous cell carcinoma
KRAS	Kirsten rat sarcoma virus
LCC	Large cell carcinoma
LUAD	Lung adenocarcinoma
LUSC	Lung squamous cell carcinoma
MAPKs	Mitogen-activated protein kinases
MCL1	MCL1 apoptosis regulator
MET	Mesenchymal-epithelial transition factor
MLH1	MutL homolog 1
MLL1/2	Mixed-lineage leukemia 1/2
MYC	Myc proto-oncogene
NTRK	Neurotrophic tyrosine receptor kinase
NSCLC	Non-small cell lung cancer
PD-1	Programmed cell death protein 1
PDAC	Pancreatic ductal adenocarcinoma
PIC	Preinitiation complex
P53	P53 tumor protein
RET	Rearranged during transfection
RBL2	Retinoblastoma-like protein 2
RNAPII	RNA polymerase II
ROS1	ROS proto-oncogene 1
SCLC	Small-cell lung cancer
SOX2	SRY-box transcription factor 2
SPT5	SPT5 transcription elongation factor
TFIIE	Transcription factor IIE
TFIIH	Transcription factor IIH
THZ1-R	THZ1-resistant
TKI	Tyrosine kinase inhibitors
TRAIL	Tumor necrosis factor-related apoptosis-inducing ligand
XIAP	X-linked inhibitor of apoptosis protein

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