Transcription associated cyclin-dependent kinases as therapeutic targets for prostate cancer

Theodora A. Constantin1,2, Kyle K. Greenland1,2, Anabel Varela-Carver1 and Charlotte L. Bevan1,2

© The Author(s) 2022

Transcriptional deregulation has emerged as a hallmark of several cancer types. In metastatic castration-resistant prostate cancer, a stage in which systemic androgen deprivation therapies fail to show clinical benefit, transcriptional addiction to the androgen receptor is maintained in most patients. This has led to increased efforts to find novel therapies that prevent oncogenic transactivation of the androgen receptor. In this context, a group of druggable protein kinases, known as transcription associated cyclin-dependent kinases (tCDKs), show great potential as therapeutic targets. Despite initial reservations about targeting tCDKs due to their ubiquitous and prerequisite nature, preclinical studies showed that selectively inhibiting such kinases could provide sufficient therapeutic window to exert antitumour effects in the absence of systemic toxicity. As a result, several highly specific inhibitors are currently being trialled in solid tumours, including prostate cancer. This article summarises the roles of tCDKs in regulating gene transcription and highlights rationales for their targeting in prostate cancer. It provides an overview of the most recent developments in this therapeutic area, including the most recent clinical advances, and discusses the utility of tCDK inhibitors in combination with established cancer agents.

Oncogene (2022) 41:3303–3315; https://doi.org/10.1038/s41388-022-02347-1

INTRODUCTION

Cyclin-dependent kinases (CDKs) are a family of serine/threonine kinases that are highly conserved across the eukaryotic genome and play fundamental roles in cell cycle regulation and transcriptional control. CDKs are traditionally separated into two major classes: cell cycle-associated CDKs (including CDK1, CDK2, CDK4 and CDK6) and transcription associated CDKs (CDK7, CDK8, CDK9, CDK12, CDK13 and CDK19). Uniquely amongst CDKs, CDK7 is a component of the human CDK-activating kinase (CAK), an important regulator of CDK activity, and has essential roles in both cell division and transcription [1].

Collectively, transcriptional CDKs (tCDKs) orchestrate the transcription cycle, a series of sequential biochemical reactions that control RNA synthesis and processing [2]. Transcriptional dysregulation is increasingly recognised as a hallmark of cancer, with transcription factors (TFs) often acting as oncogenes driving proliferation and survival [3]. This addiction to certain transcriptional programs uncovered new therapeutic vulnerabilities which spotlighted tCDKs as attractive new targets for several types of cancer, including advanced castration-resistant prostate cancer (CRPC). In CRPC, the transcriptional addiction to the androgen receptor (AR, a ligand-activated transcription factor and main therapeutic target) seen in early-stage disease remains a major driver of tumour growth, but available androgen deprivation therapies, all of which effectively target the ligand binding domain of AR, fail to prevent disease progression [4]. Relapse and metastasis are the major cause of death in patients, highlighting an unmet need for novel treatment strategies in CRPC. In this context, targeting of tCDKs, which play crucial roles in gene transcription as well as AR signalling, provides a novel therapeutic strategy for both hormone-naïve and castration-resistant disease.

ROLE OF TCDKS IN EUKARYOTIC TRANSCRIPTION

Transcription of protein-coding genes is mediated by RNA polymerase II (Pol II). Pol II is a multiprotein complex that transcribes DNA into mRNA via a series of highly coordinated events, collectively known as the transcription cycle. Broadly, the Pol II transcription cycle can be divided in four stages: assembly of the preinitiation complex, promoter escape, elongation, and termination [2]. The coordinated activity of tCDKs allows an orderly transition between the stages of the transcription cycle; they regulate transcription by phosphorylating the carboxy-terminal domain (CTD) of RPB1, the largest subunit of Pol II, as well as other TFs (Table 1). The Pol II CTD is composed of up to 52 heptapeptide repeats (Tyr-Ser-Pro-Thr-Ser-Pro-Ser) and serves as a binding structure for the other nuclear factors involved in transcription [5, 6]. Patterns of CTD phosphorylation differ at different stages of transcription and allow for the timely recruitment of factors important for mRNA elongation and maturation (Fig. 1) [6].

CDK7 is a “master regulator” of transcription

CDK7 regulates Pol II-mediated transcriptional initiation and pausing, in addition to indirectly promoting transcript elongation via other tCDKs through its CAK activity. In eukaryotes,

1Imperial Centre for Translational and Experimental Medicine, Department of Surgery and Cancer, Imperial College London, Hammersmith Hospital, London, UK. 2These authors contributed equally: Theodora A. Constantin, Kyle K. Greenland. ✉email: charlotte.bevan@imperial.ac.uk

Received: 21 March 2022 Revised: 21 April 2022 Accepted: 4 May 2022
Published online: 14 May 2022
Table 1. Substrates of transcription associated CDKs.

| Transcriptional CDK (partner cyclin/other partner protein) | Substrate(s) | Residue(s) | Downstream effect(s) | Reference(s) |
|----------------------------------------------------------|--------------|------------|----------------------|--------------|
| CDK7 (cyclin H, MAT1)                                     | RPB1 (C-terminal domain) | Ser5       | Facilitates promoter escape | [7, 8]       |
|                                                          | RPB1 (C-terminal domain) | Ser7       | Recruitment of RPAP2, transcription of snRNA genes | [9]         |
| CDK9 (T-loop domain)                                      | RPB1 (C-terminal domain) | Ser175     | Promotes recruitment of BRD4 | [10]        |
|                                                          | RPB1 (C-terminal domain) | Thr186     | Enhanced activity | [11]        |
| CDK12 (T-loop domain)                                     | RPB1 (C-terminal domain) | Thr893     | Enhanced activity | [12]        |
| CDK13 (T-loop domain)                                     | RPB1 (C-terminal domain) | Thr871     | Enhanced activity | [12]        |
| MED1 (C-terminal region)                                  | RPB1 (C-terminal domain) | Thr1457    | Recruitment to chromatin association with AR and the transcription machinery | [13]        |
| SF3B1                                                    | 18 putative sites (residues 207-434) |              | Affects association with splicing speckles | [12]        |
| U2AF2                                                    | Unknown      | Unknown    | Unknown              | [12]        |
| DNA-binding TFs: AR, E2F1, ERα, Ets1, p53, PPARγ2, RARα, YAP/TAZ, SF1 | Ser515 AR, Ser403/Thr433 E2F1, Ser118 ERα, Thr38 Ets1, Ser33 p53, Ser121 PPARα, Ser122/Thr21 PPARγ2, Ser77 RARα, Ser77/Ser79 RARγ, Ser128/90 YAP/TAZ, Ser203 SF1 | Promotes activity and/or regulation of protein turnover | [14]        |
| CDK8/CDK19 (cyclin C)                                     | Several validated DNA-binding TFs, Mediator subunits, and chromatin regulators (e.g. STAT1, MED12, MED13, SIRT1) | Ser727 STAT1, Ser688 MED12, Ser749 MED13, Thr530 SIRT1 | Context-dependent effects; potentiation of transcriptional activation | [15]        |
| CDK9 (cyclin T1)                                          | RPB1 (C-terminal domain) | Ser2       | Promotes transcription elongation | [16]        |
|                                                          | DSIF (Spt5 subunit) | Thr4       | Facilitates promoter-proximal pause release of Pol II | [17]        |
|                                                          | NELF (NELF-E subunit) | Ser81, Ser294 | Facilitates promoter-proximal pause release | [18]        |
|                                                          | XRN2          | Thr439     | Enhanced cleavage of the RNA transcript from Pol II | [19]        |
|                                                          | DNA binding TFs: AR, ERα | Ser81, Ser294 | Transcriptional activation in response to ligand | [20, 21] |
| CDK11 (cyclin L)                                          | AR (N-terminal domain) | Ser308     | Repression of AR transcription | [22]        |
| CDK12/CDK13 (cyclin K)                                    | RPB1 (C-terminal domain) | Ser2       | Promotes elongation and the use of distal 3′ transcription termination sites | [23, 40] |

CDK cyclin-dependent kinase, RPB1 DNA-directed RNA polymerase II subunit rpb1, MED1 mediator complex subunit 1, SF3B1 splicing factor 3b subunit 1, U2AF2 small nuclear RNA auxiliary factor 2, TF transcription factor, AR androgen receptor, ERα oestrogen receptor alpha; Ets1 ETS proto-oncogene 1, PPAR peroxisome proliferator-activated receptor alpha, RAR retinoic acid receptor, YAP yes-associated protein 1, TAZ transcriptional coactivator with PDZ-binding motif, SF1 splicing factor 1 DSIF DRB sensitivity inducing factor, NELF negative elongation factor, XRN2 5′-3′ exoribonuclease 2, RPAP2 RNA polymerase II-associated protein 2, BRD4 bromodomain-containing protein 4.
transcription initiation begins with the assembly of the preinitiation complex. The minimal preinitiation complex includes Pol II and six general TFs: TFIIA, TFIIB, TFIID, TFIIE, TFIIF, and TFIIH [7]. TFIIH consists of two subcomplexes: the core complex, comprising ATP-dependent helicases, and the CAF complex, which harbours the kinase activity of CDK7 [8]. In addition, the Mediator complex, which is generally required for transcription by Pol II, anchors the preinitiation complex to gene-specific upstream enhancers [9]. At the transcription start site (TSS), following DNA unwinding by helicases, Pol II must be released from the preinitiation complex and dissociate from the Mediator complex. This process, termed promoter escape, is facilitated by the phosphorylation of the Pol II C-terminal domain (CTD) at serine 5 (Ser5) and serine 7 (Ser7) by CDK7, which promotes recruitment of pre-mRNA 5′-capping enzymes. Transcription is provisionally paused downstream of the transcription start site by the association of two negative factors, DRB sensitivity-inducing factor (DSIF) and negative elongation factor (NELF). Bromodomain-containing protein 4 (BRD4) and the positive transcription elongation factor (P-TEFb), consisting of CDK9 and cyclin T, are recruited to acetylated chromatin. CDK7 activates CDK9 through T-loop phosphorylation, which in turn mediates promoter-proximal pause release by phosphorylating DSIF, NELF, and the Pol II CTD at serine 2 (Ser2). Progression from the transcriptional start site (TSS) across the gene body and productive elongation are maintained by the differential phosphorylation of the Pol II CTD at Ser2, Ser5, and Ser7 by CDK9 and CDK12/CDK13. The pattern of CTD phosphorylation contributes to the recruitment of splicing and chromatin remodelling factors. Termination is regulated by CDK12 which promotes the use of distal 3′ transcription termination sites and recruitment of cleavage and polyadenylation (Poly A) factors. The graph underneath depicts relative abundance of Pol II Ser-CTD modifications across protein-coding genes, determined by chromatin immunoprecipitation (ChIP)-seq investigations. Created with BioRender.com.
trimethylated H3K4 modifications play an important role in pre-mRNA splicing [19], it is possible that CDK7 also regulates several splicing and RNA processing factors. Using quantitative phosphoproteomics, a recent study showed that the largest subunit of the spliceosome factor 3b, complex, SF3B1, and the U2 auxiliary factor, U2AF2, are CDK7 substrates [20]. Further supporting this, inhibition of CDK7 activity using the covalent inhibitor SY-351 induced widespread changes in alternative mRNA splicing in vitro [20].

TFIIH also functions in nucleotide excision repair (NER). TFIIH is recruited to sites of DNA damage, where it promotes incision and exclusion of DNA bases. Then, xeroderma pigmentosum A catalyses the release of CAF from the core TFIIH complex, facilitating effective NER of damaged bases [21]. Following repair, CAF re-associates with TFIIH, enabling transcription to proceed [22]. Previous research has shown that inhibition of CAF activity improves repair efficiency, indicating that CAF may be a negative regulator of NER [23].

**CDK9 stimulates transcript elongation**

As alluded to above, CDK9 associates with cyclin T1 to form P-TEFb, a potent general transcription factor that is maintained under stringent negative regulation by the 7SK small nuclear ribonucleoprotein (snRNP) [24]. The canonical 7SK snRNP complex contains the highly abundant non-coding 7SK snRNA, which is stabilised by La Ribonucleoprotein 7 (LARP7) and methylphosphosphate capping enzyme (MePCE). The 7SK snRNP complex functions as a scaffold where P-TEFb is inactivated through association with hexamethylen-bis-acetamide inducible proteins 1/2 (HEXIM1 and/or HEXIM2) [25]. The chromatin-tethered 7SK snRNP complex represents a major reservoir of transcriptionally inactive P-TEFb and serves as a source of P-TEFb to facilitate Pol II escape. Release of P-TEFb occurs when Bromodomain-containing protein 4 (BRD4) is recruited to TSS via histone acetylation and competes with the inhibitory HEXIM/7SK complex [26].

Promoter-proximal pausing of Pol II is initiated by the association of two negative factors, DRB sensitivity-inducing factor (DSIF) and negative elongation factor (NELF) [27]. P-TEFb phosphorylates the Spt5 subunit of DSIF, converting it to a positive elongation factor [28] and causing dissociation of NELF from Pol II [27]. The transition to productive elongation is then mediated by P-TEFb, which phosphorylates Ser2 residue on the CTD of Pol II [29] (Table 1). Additionally, CDK9 also phosphorylates Thr4 of the Pol II CTD; this is required for histone mRNA 3' end processing by facilitating the recruitment of 3’ processing factors to histone genes [30].

Emerging evidence suggests a role of CDK9 in regulating transcription termination (Table 1). A high-throughput screen for CDK9 substrates identified over 100 proteins, a large majority of which were implicated in transcription and RNA catabolism [31]. Xrn2, a nuclear 5'-to-3' exoribonuclease required for Pol II termination, was validated as a CDK9 substrate, suggesting that CDK9 directly regulates a transcription termination pathway. CDK9 activity is also essential for the deposition of histone H2B monoubiquitylation, through a CTD-dependent mechanism [32]. In its absence, Pol II continues transcription until an alternative downstream polyadenylation site is reached. Furthermore, CDK9 inhibitors decrease transcription downstream of the polyadenylation site, supporting the idea that CDK9 activity plays a role in transcription termination [33] (Fig. 1).

**CDK8 and CDK19 are Mediator-associated kinases**

CDK8 is a transcriptional kinase which associates with regulatory genomic elements together with the Mediator complex. CDK8 forms the CDK8 kinase module together with cyclin C, MED12, and MED13. Cyclin C and MED12 activate the CDK8 kinase function, while MED13 enables association with the Mediator complex [34]. Three components of the CDK8 module, namely CDK8, MED12, and MED13, have paralogs that have arisen from gene duplications. These are CDK8-like (CDK19), MED12-like (MED12L), and MED13-like (MED13L), respectively. These paralogs can form part of the CDK8 kinase module but are mutually exclusive of each other, enabling the assembly 8 different CDK modules, always together with cyclin C [35]. Importantly, the existence of several CDK-Mediator complexes indicates potential functional distinctions.

As the Mediator complex is usually required for transcription by Pol II in mammalian cells [9], disruption of CDK8/CDK19 function would be predicted to have a global effect on transcription. However, genetic and pharmacological inhibition of CDK8/CDK19 has been shown to affect only subsets of genes, which differ between cell types [36, 37]. It could be speculated that this cell type-specificity of Mediator kinases is determined by chromatin structure and histone modifications, which give rise to cell type-specific enhancers, TF binding patterns, and enhancer-promoter communication. Supporting this idea, in a phosphoproteomics study, inhibition of CDK8/CDK19 revealed that many substrates are DNA-binding TFs or chromatin regulators [38] (Table 1).

**CDK12 and CDK13 multi-task to tune transcription**

CDK12 and CDK13 are two evolutionarily-related kinases that associate with cyclin K and display Pol II CTD kinase activity, particularly when Ser7 CTD residue is pre-phosphorylated [39]. Despite the structural similarity of their kinase domain and partnering with the same cyclin, CDK12 and CDK13 regulate distinct biological processes. CDK12 inhibition primarily affects the expression of genes involved in the DNA damage response, although suppression of super-enhancer-associated genes has been observed at high inhibitor concentrations [40]. CDK12 also affects the processing of nascent RNA, by promoting the use of distal 3’ transcription termination sites and suppressing intronic polyadenylation, resulting in the production of full-length gene transcripts [41]. Notably, genes implicated in the DNA damage response are longer and display more intronic polyadenylation sites compared to other expressed genes [42], which could explain how depletions of CDK12 activity selectively alters their expression. Emerging evidence also suggests a role for CDK12 in controlling splicing and regulating the expression of splicing factors. CDK12 has been shown to interact with several components of the core spliceosome and regulators of constitutive and alternative splicing and has even been proposed as a bona fide component of the splicing machinery [43]. Taken together, loss of CDK12 activity affects transcription elongation, RNA processing, and termination, and may also lead to splicing defects and genome instability, although the mechanism underlying the specificity for certain genes requires further research.

The role of CDK13 in transcription is less well understood but recent evidence shows that it is distinct from that of CDK12. Although it has been reported to have Pol II CTD kinase activity (Fig. 1), knockdown of CDK13 leads to less CTD phosphorylation alteration than knockdown of CDK12 [39]. Furthermore, research indicates CDK13 preferentially regulates snRNA and small nucleolar RNA genes that guide posttranscriptional modifications of other RNAs, primarily ribosomal RNAs, as well as some genes involved in mitochondrial energy metabolism [44].

**Other transcriptional CDKs**

CDK10 is activated by the partner cyclin M and controls transcription mediated by ETS2, a member of the ETS family of oncogenic TF, by phosphorylation and promoting protosomal degradation [45, 46]. Therefore CDK10/cyclin M can negatively regulate ETS2 transcription, suggesting a tumour suppressor role. CDK11 is activated by L-type cyclins and has roles in alternative splicing, where it can influence splice site selection [47]. Additionally, CDK11 has an important role in regulating the expression of replication-dependent histone genes by promoting elongation and 3’-end processing [48]. Replication-dependent
The coordinated activity of tCDKs appears to be crucial for the transcriptional activation of AR, indicating that these kinases would be good therapeutic targets for CRPC. Several tCDKs can directly phosphorylate AR to regulate its stability, nuclear localisation, or/and transcriptional output (Table 1 and Fig. 2). Phosphorylation of Ser515 in the N-terminal domain of AR by CDK7 is required for both maximal transactivation and for optimal cyclical ubiquitination, proteasomal degradation and re-recruitment of AR to gene promoters [53, 54]. Recent studies have shown that the Mediator Complex Subunit 1 (MED1, also known as TRAP220/DPRI205) can undergo CDK7-dependent phosphorylation at Thr1457 which promotes engagement of AR at enhancer and super-enhancer sites, and transcription of AR regulated genes [55]. Phosphorylation of chromatin-bound AR at Ser81, the major site that is modified in response to androgen treatment, is primarily mediated by CDK9 [56]. Ser81 phosphorylation enhances recruitment of the histone acetyltransferase (and AR coactivator) p300 and of BRD4, which further releases P-TEFb, creating a positive feedback loop that maintains transcription of AR target genes [57]. In addition, CDK11 can phosphorylate AR at Ser308, although this modification has a negative effect on AR-mediated transactivation [58].

Recently published in vivo studies demonstrated the anti-tumour activity of compounds targeting CDK7, CDK9 and CDK8/CDK19 in CRPC models, with mechanistic explorations consistently highlighting suppression of oncogenic AR transcription as a downstream effect of treatment. Inhibition of CDK7 attenuated AR signalling regardless of enzalutamide sensitivity status, by preventing association with oncogenic super-enhancers in vitro, and led to potent growth suppression in the VCaP CRPC xenograft model, which harbours TMPRSS2-ERG gene fusion and expresses several constitutively active AR splice variants [55]. Screening for novel compounds that could modulate the transcriptional output of AR returned a lead, the molecular target of which was identified through a CRISPR screen as a kinase that is essential for prostate cancer cell survival [61]. Suppression of CDK12 activity repressed AR signalling and induced apoptosis in vitro. Collectively, these studies strengthen the view of CRPC as a transcriptionally addicted cancer type and highlight tCDKs as promising targets to prevent oncogenic AR signalling in relapsed tumours.

**TCDK inhibitors as cancer therapeutics**

Early drug discovery efforts focused on designing inhibitors that targeted the ATP binding pocket, conserved across the CDK family [62]. The first pan-CDK inhibitor to enter clinical trials was flavopiridol, a semi-synthetic flavone derivative, followed by seliciclib, a purine-based compound [63]. However, the promiscuity of these two inhibitors likely contributed to their failure in the clinic, following numerous patient toxicities and challenges in establishing an accurate pharmacodynamic profile in vivo [63]. The initial setbacks associated with pan-CDK inhibitors paved the foundation for the development of second-generation selective CDK inhibitors. Thus far, CDK4/6 inhibitors (CDK4/6i) have proved the most promising, with three inhibitors (palbociclib, ribociclib, and abemaciclib) currently approved by the U.S. Food and Drug Administration (FDA) for oestrogen receptor (ER)-positive breast cancer treatment. Although beyond the scope of this review, the promising antioncogenic activity combined with the clinical success of CDK4/6i galvanized support for the development of highly selective inhibitors for other CDKs. The next sections will provide an overview of the current tCDK-specific inhibitors that histone genes have fundamental roles in cell division, suggesting CDK11 may have an important role in cancer.
have good drug-like properties and are, therefore, promising candidates for clinical development (Table 2).

**CDK7-specific inhibitors**

The first highly-selective CDK7 inhibitor, BS-181 was derived from seliciclib using a modelling-based structural design [64]. Preclinical studies using MCF-7 breast cancer cells demonstrated good target engagement, resulting in cell cycle arrest and apoptosis in vitro, and suppression of subcutaneous xenograft growth in vivo [64]. Despite promising antioncogenic effects, poor cell permeability and bioavailability impeded the progression of BS-181 into clinical trials. Nearly 10 years later, structural refinements of BS-181 yielded the first orally bioavailable CDK7 inhibitor, ICEC0942, with 15-230-fold greater selectivity for CDK7 over other CDKs [65]. Preclinical studies showed that ICEC0942 inhibits proliferation in numerous cancer cell types in vitro but also demonstrated that ER-positive cells were especially susceptible to ICEC0942 as a single agent or in combination with endocrine therapies, providing a rationale for the use of CDK7 inhibitors in the treatment of ER-positive breast cancer [65]. ICEC0942/CT7001, now renamed samuraciclib, was licenced to Carrick Therapeutics and is currently in phase I/II clinical studies for advanced solid malignancies as single agent or in combination with standard therapy for specific participant groups, including triple-negative breast cancer (TNBC) and CRPC cohorts (NCT03363893).

THZ1 is a covalent CDK7 inhibitor identified through cell-based screening and kinase selectivity profiling [66]. THZ1 irreversibly targets a cysteine residue (Cys312) located outside of the kinase domain of CDK7, resulting in allosteric inhibition of CDK7 activity. However, THZ1 has a relatively short half-life in vivo [66], and later studies indicated that it covalently inhibits CDK12 and CDK13 in addition to CDK7 [67]. With the aim of improving specificity and stability, several analogues of THZ1 have been developed. A hybrid strategy combining the covalent warhead of THZ1 with a pyrrolidino-pyrazole core produced YKL-5-124. In vitro studies indicated that YKL-5-124 had potent effects on the cell cycle, but did not significantly affect global basal transcription [68]. However, in preclinical models of small cell lung cancer, YKL-5-124 induced genomic instability and triggered an inflammatory response, resulting in potentiation of anti-PD-1 therapy [69]. Although not yet in clinical trials, YKL-5-124 provides a link between CDK7 inhibition and augmented antitumour immunity, and therefore represents a promising new approach in cancer immunotherapy. Recently, Syros Pharmaceuticals have announced the clinical development of a new orally available ATP-competitive CDK7 inhibitor, SY-5609 [70], after terminating previous studies using the covalent compound SY-1365 [71]. Preclinically, SY-5609 presents with favourable antitumor activity in ER-positive breast cancer [72], TNBC and ovarian cancer models [70]. It is currently being assessed in a phase I dose-escalation study (NCT04247126).
| Name(s) | Inhibitor Type | Intended Therapeutic Target | Major Biological Target(s) IC50 (nM) | Company | Malignancy Type(s) | Clinical Trial Status |
|---------|----------------|-----------------------------|-------------------------------------|---------|-------------------|----------------------|
| CT7001 (ICEC0942; Samuraciclib) | Non-covalent | CDK7 | CDK1 = 1800; CDK2 = 620; CDK4 = 4900; CDK5 = 9400; CDK6 = 3400; CDK7 = 40; CDK9 = 1200 | Carrick Therapeutics | Advanced Solid Malignancies | Phase I/II NCT03363893 (Active) |
| SY-1365 | Covalent | CDK7 | CDK7 = 20 | Syros Pharmaceuticals | Advanced Solid Tumours | Phase I NCT03134638 (Terminated) |
| SY-5609 | Non-covalent | CDK7 | CDK2 = 2900; CDK7 = 0.06; CDK9 = 970; CDK12 = 770 | Syros Pharmaceuticals | Advanced Solid Tumours | Phase I NCT04247126 (Recruiting) |
| XL102 (AUR102) | Covalent | CDK7 | Not disclosed | Exelixis | Advanced Solid Tumours | Phase I NCT04726332 (Recruiting) |
| LY3405105 | – | CDK7 | CDK1 = 20000; CDK2 = 20000; CDK4 = 2830; CDK6 = 8079; CDK7 = 92.8; CDK9 = 6200; CDK12 = 14780 | Eli Lilly and Company | Advanced Solid Tumours | Phase I NCT03770494 (Completed) |
| BAY1143572 | Non-covalent | CDK9 | CDK9 = 13; CDK3 = 890; CDK2 = 1000; CDK1 = 1100; CDK5 = 1600 | Bayer | Advanced Acute Leukaemia | Phase I NCT02345382 (Completed) |
| VIP152 (BAY1251152) | Non-covalent | CDK9 | CDK2 = 360; CDK9 = 3 | Vincerx Pharma | Advanced Hematological Malignancies | Phase I NCT02745743 (Completed) |
| AZD4573 | Non-covalent | CDK9 | CDK9 = < 4 | AstraZeneca | Relapsed/Refractory Haematological Malignancies | Phase I NCT03263637 (Completed) |
| KB-0742 | Non-covalent | CDK9 | CDK9 = 6 | Kronos Bio | Relapsed or Refractory Solid Tumors; Non-Hodgkin Lymphoma | Phase I NCT04718675 (Recruiting) |
Table 2. Name(s) Inhibitor Type Intended Major Biological Target(s) IC50 (nM)* Therapeutic Target

| Company | Clinical Trial Status | Malignancy Type(s) | Major Biological Target(s) (IC50a) | Intended Therapeutic Target | Inhibitor Type |
|---------|-----------------------|--------------------|-----------------------------------|-----------------------------|----------------|
| GenFleet Therapeutics | Phase I | Relapsed/Refractory hematologic malignancies | CDK8 = 17.3; CDK19 = 4.2 | Non-covalent | Not disclosed |
| Biocad | Phase I | Locally Advanced or Metastatic ER positive HER2-negative Breast Cancer | CDK8 = 10.4 | Covalent | RVU120 (SEL120) |
| Ryvu Therapeutics | Phase I | Acute Myeloid Leukemia; High-risk Myelodysplastic Syndrome | CDK8 = 4.4; CDK19 = 10.4 | Covalent | GVH009 |
| Biocad | Phase I | Metastatic or Advanced Solid Tumours | CDK8 | Covalent | GVH009 |

*IC50 data has been listed for CDK1, 2, 3, 4, 6, 7, 9, and 12 derived from in vitro kinase activity studies. IC50 values are determined by activity assay. CDK, cyclin-dependent kinase; ER, oestrogen receptor.

**Continued...**

in patients with advanced solid tumours, with the most recent update from the company reporting good clinical activity. AUR102 is a recently described orally bioavailable CDK7-selective inhibitor with preclinical activity in models of breast cancer, prostate cancer, and lymphoma [73]. AUR102, now renamed XL102, was licensed by Exelixis from Aurigene and is undergoing clinical testing for advanced or metastatic solid cancers as single-agent or combination therapy (NCT04726332). Another CDK7 inhibitor, LY3405105, developed by Eli Lilly, entered clinical development for patients with advanced solid tumours, however the phase I study was very recently terminated due to lack of efficacy (NCT03770494).

**CDK9-specific inhibitors**

Among the first CDK9 inhibitors available, flavopiridol has been studied most extensively. Preclinical evaluations showed potent antiproliferative effects in a range of haematological malignancies [74]. In recent years, more selective CDK9 inhibitors have been developed, of which five were entered into clinical trials: BAY1143572, BAY1251152, AZD4573, KB-0742, and GFH009.

BAY1143572 (atvecumlib), the first highly selective CDK9 inhibitor described by Bayer, exhibited marked tumour growth inhibition in preclinical models of acute myeloid leukaemia [75] and adult T-cell leukaemia/lymphoma [76]. BAY1143572 was trialled in two cohorts of patients with advanced acute leukaemia (NCT02345382) and advanced solid tumours (NCT01938638). However, both studies were terminated early as a therapeutic window could not be identified, and the clinical development program for BAY1143572 was discontinued. Bayer also sponsored two phase I studies using BAY1251152 (later renamed VIP152), a follow-up more potent CDK9 inhibitor. The first trial, in patients with advanced blood cancer, failed to show clinical efficacy despite evidence of target engagement (NCT02745743) [77]. The second trial (NCT02635672) showed a manageable safety profile and signs of antitumour activity [78], particularly in MYC-driven lymphoma and solid tumours [79]. This study is still ongoing, although sponsorship was transferred to Vincrx Pharma. Additionally, Vincrx Pharma recently announced a new phase I trial to evaluate VIP152 in relapsed/refractory chronic lymphocytic leukaemia or Richter’s Transformation (NCT04978779).

A structure-based approach led to the identification of AZD4573, a highly potent CDK9 inhibitor with over 25-fold selectivity for CDK9 over other CDKs, and broad antitumor activity across preclinical hematologic cancer models [80, 81]. A phase I trial of AZD4573 in patients with relapsed or refractory haematological malignancies was recently completed (NCT03263637, pending results reporting), while a phase I/Ii study has recently started recruiting patients with advanced blood cancers to be treated with AZD4573 in combination with acalabrutinib (NCT04630756). In addition, a phase II trial exploring the safety and efficacy of AZD4573 as monotherapy or in combination with anti-cancer agents for patients with relapsed/refractory peripheral T-cell lymphoma or classical Hodgkin lymphoma was announced at the end of 2021 (NCT05140382).

The CDK9 inhibitors mentioned have short in vivo half-lives (<1 h) and limited activity in preclinical models of solid tumours, therefore they are primarily trialled being against haematological cancers. Kronos Bio’s recently discovered KB-0742, a well-tolerated, orally bioavailable CDK9 inhibitor, significantly reduces tumour burden in models of prostate cancer in vivo [59]. This provided compelling support for developing KB-0742 as therapeutic for solid cancers. Encouragingly, interim analysis of Kronos Bio’s ongoing phase I/I trial of KB-0742 (NCT04718675) demonstrated dose-dependent target engagement and a terminal half-life of 24 h in patients with advanced solid tumours.

Limited information is available about GenFleet Therapeutics’ highly selective CDK9 inhibitor, GFH009, other than the announcement of a phase I clinical trial for haematological malignancies (NCT04588922).
CDK12/13-specific inhibitors

Three CDK12/13-specific inhibitors have been described, although none have progressed into clinical evaluation. THZ531 and the optimised BSJ-01-175, both derived from THZ1, are covalent CDK12/13 inhibitors [67, 82], while SR-4835 is an irreversible ATP competitive inhibitor [83]. To date, in vivo preclinical studies using these inhibitors showed antitumour activity in models of Ewing sarcoma and TNBC, and demonstrated that CDK12/13 inhibition may improve the efficacy of DNA-damaging chemotherapy and PARP inhibitors [82, 83]. Notably, deleterious loss-of-function CDK12 mutations are frequently observed in cancer, including in 3-7% of patients with metastatic CRPC [84]. While associated with aggressive disease and poor prognosis, CDK12 alterations also induce a BRCAness phenotype due to perturbation of the homologous recombination repair pathway. However, in a recent study, the transcriptional alterations mediated by small molecule CDK12/13 inhibitors differed from those mediated by loss-of-function CDK12 mutations [61], suggesting selective CDK12/13 inhibitors may function through a distinct mechanism, which warrants further exploration.

CDK8/19-specific inhibitors

Cortistatin A is a naturally occurring compound identified as the first selective CDK8 inhibitor in 2015 [37]. Since then, numerous small molecule CDK8/19 inhibitors have been described, including Cmpd3 and Cmpd4, Senexin B, and SEL120. Preclinical studies using Cmpd3 and Cmpd4, two chemically distinct CDK8/19 inhibitors, showed encouraging antitumour activity in a number of tumour models but poor toxicity profile, with considerable weight loss and multiple systemic toxicities, including lethality [85]. This raised concerns that inhibiting CDK8/19 does not provide sufficient therapeutic window, although later reports suggested the adverse events to be unrelated to CDK8/19 inhibition, pointing to off-target inhibition as the most likely cause of toxicity [86]. In 2017, Senexin B (renamed BCD-115) was the first selective CDK8/19 inhibitor to enter a phase I clinical trial which was completed (NCT03065010). The compound was evaluated for the treatment of women with ER-positive, human epidermal growth factor receptor-2 (HER2)-negative, locally advanced or metastatic breast cancer.

SEL120 is an orally bioavailable, highly potent, ATP-competitive CDK8/19 inhibitor which suppresses growth in vivo in models of acute myeloid leukaemia [87]. In April 2020, the FDA granted orphan drug status to SEL120 (renamed RVU120) for the treatment of patients with acute myeloid leukaemia. The first trial using RVU120 began in 2019 (NCT04021368) but was paused April 2021 due to reports of a serious adverse effect potentially related to RVU120 administration that resulted in the death of a patient. In July 2021, the FDA lifted the partial clinical hold on this study and Ryvu Therapeutics, the sponsoring company, announced the beginning of parallel phase I/II study of RVU120 as single agent in patients with relapsed or refractory metastatic or advanced solid tumours (NCT05052255).

EMERGING COMBINATION STRATEGIES USING CDK INHIBITORS

Although many of the inhibitors mentioned have shown significant antitumour activity as single agents, the dynamic nature of advanced tumours often demands inhibition of multiple...
targets to limit disease reoccurrence. As such, efforts have also focused on developing tCDK inhibitors as adjuvant therapies (Fig. 3). Finding efficacious combination strategies with established anticancer therapies can provide additive or synergistic activity, allowing dose reduction and minimising the risk of treatment-related toxicity. To date, none of the strategies below have been trialled in prostate cancer, but some are already undergoing clinical assessment in other cancer types.

Endocrine therapies
Due to the role of tCDKs in modulating the transcriptional activity of hormone receptors, a potentially promising therapeutic strategy is combining tCDK inhibitors with endocrine therapies. Preclinical studies of C7T7001 in breast cancer models provided evidence that the combination of CDK7 inhibitors with tamoxifen is superior to either monotherapy [65]. In August 2021, Carrick Therapeutics announced it was granted Fast Track designation for C7T7001 in combination with the antiestrogen fulvestrant for the treatment of CDK4/6i-resistant hormone receptor-positive, HER2-negative advanced breast cancer and that it will begin evaluating C7T7001 in combination with giredestrant, a next-generation selective oestrogen receptor degrader, in collaboration with Roche (NCT04802759).

Preclinical evidence also supports combination use of tCDK inhibitors with antiandrogens in prostate cancer. Inhibition of CDK12 was shown to synergise with antiandrogens through a mechanism involving decreased acetylation of histone H3K27 at AR:FOXA1 binding sites [51]. In addition, CDK7, CDK9 and CDK8/19 inhibitors are potential candidates for use in combination with antiandrogens, since inhibition of these kinases was shown to suppress AR signalling in disease-relevant models [55, 59, 60].

**DNA and DNA-repair targeted therapies**

The activity of CDK7 and CDK12/13 is fundamental to maintaining genome stability and repairing DNA damage following genomic insult. Consistently, CDK7 inhibition by YKL-5-124 has been shown to elicit genomic instability in small cell lung cancer models, while CDK12/13 inhibition has been shown to provoke a “BRCA-ness” phenotype in TNBC [69, 83]. Furthermore, CDK7 inhibition synergises with p53-activating agents, including 5-fluorouracil, and induces apoptosis in colorectal cancer cells [88], while combining CDK12/13 inhibition with DNA-damaging chemotherapy, including cisplatin, irinotecan, doxorubicin and with the PARP inhibitor olaparib was shown to augment anticancer activity in TNBC cells [83]. Consequently, it is foreseeable that combining CDK7 and CDK12/13 inhibitors alongside DNA damage-inducing agents may further promote genomic instability. Carrick Therapeutics announced it was granted Fast Track designation for the CDK7 inhibitor C7T7001 in combination with chemotherapy for the treatment of locally advanced or metastatic TNBC, while Syros Pharmaceuticals announced it will begin clinical investigation of the CDK7 inhibitor SY-5609 in combination with chemotherapy for the treatment of tumour-bearing mice with THZ1, a CDK7/CDK12/13 inhibitor, before infusion with CAR T-cells attenuated cytokine release by suppressing transcription of inflammatory genes, thus preventing the associated systemic toxicity [91].

**Other targeted therapies**

Receptor tyrosine kinase inhibitors used in combination with tCDK inhibitors include epidermal growth factor receptor (EGFR) and HER2 inhibitors. In breast cancer models, the EGFR inhibitor erlotinib displayed synergy with THZ1 and with the dual cdc7/CDK9 inhibitor PHA-776491 [92, 93], with more lines of evidence suggesting CDK7 and CDK9 inhibitors could sensitisie resistant cancer cells to EGFR-targeted therapy [93, 94]. A similar effect was seen with THZ1 and the HER2 inhibitor lapatinib, which displayed synergistic effects when combined in breast cancer models independently of HER2 inhibitor-resistance status [95].

Venetoclax is a selective inhibitor of the anti-apoptotic protein B-cell lymphoma 2 (Bcl-2) currently used in haematological cancers displaying increased Bcl-2 expression. Venetoclax has been investigated in combination with several CDK9-specific inhibitors, including AZD4573 and A-1592668, and voruciclib, a flavopiridol-derivative with improved specificity for CDK9, with combination therapy showing superior efficacy to either agent alone [80, 96, 97]. Mechanistically, it has been suggested that CDK9 inhibitors enhance venetoclax activity by inhibiting transcription of anti-apoptotic proteins, thereby inducing apoptosis more efficiently [80]. In addition, to CDK9 inhibitors, the selective CDK7 inhibitor SY-1365 was also synergised with venetoclax in haematological cancers through a similar mechanism involving downregulation of anti-apoptotic proteins [71].

Recent work has also highlighted the potential use of tCDK inhibitors in combination with epigenetic drugs, including Bromodomain and Extra-Terminal (BET) motif protein inhibitors (e.g., JQ1, which synergises with CDK7 inhibition in models of ovarian cancer [98], neuroblastoma [99], and iBET-151, which synergises with CDK9 inhibition in models of leukaemia [100], and histone deacetylase inhibitors (e.g., panobinostat, which synergised with THZ1 in models of diffuse intrinsic pontine glioma [101]). In addition, combination of BRD4 inhibitors with CDK7 or CDK9 inhibitors is envisaged to effectively target AR super-enhancer addiction in CRPC [102], although preclinical studies addressing this are currently lacking.

**Co-targeting of CDKs**

Although limited evidence is available to date, exploring the ability of CDK inhibitors to act complementarily to one another is highly warranted. This is especially promising where different CDKs function together to modulate fundamental cellular processes, as is the case of the Pol II CTD kinases CDK7, CDK9 and CDK12/13 regulating transcription. In line with this, co-targeting of CDK7 and CDK9 synergistically downregulated
expression of the oncogene MYC and the anti-apoptotic protein MCL-1 and induced apoptosis through p53 activation in models of acute myeloid leukaemia [103]. In metastatic prostate cancer displaying transcriptional addiction, it can be envisaged that treatment with a combination of CDK7, CDK9, and/or CDK12/CDK13 inhibitors may lead to potent suppression of oncogenic transcription, since all of these tCDKs have established AR signalling and tumour-promoting roles in relevant disease models [55, 59, 61].

In addition, co-targeting of CDK7 along with cell cycle CDKs may be a strategy to prevent therapy resistance. A genome-wide CRISPR knock-out screen in parental and CDK4/6i-resistant MCL-1 and induced apoptosis through p53 activation in models of transcription, since all of these tCDKs have established AR signalling and tumour-promoting roles in relevant disease models [55, 59, 61].

CONCLUSIONS

In summary, tCDKs have central roles in efficient gene transcription. As well as being a requisite process in all cells, transcription is often hyperactive in many cancer types, which could be described as transcriptionally addicted. Therefore, tCDKs are emerging as promising cancer therapeutic targets and selective tCDK inhibitors have rapidly advanced in clinical trials as single agents against a wide range of tumour types. Although these inhibitors are rapidly becoming accepted as safe and specific ways to target cancer cells, clinical trial results reported to date have been mixed. This is in part due to the suboptimal selectivity profiles of first-generation tCDK inhibitors, but may also be due to incomplete understanding of the genetic and microenvironmental factors that influence tumour response to tCDK inhibition. Moreover, possible resistance mechanisms that may emerge as result of selective targeting of tCDKs are only now beginning to be identified. Notwithstanding, the potential for more selective compounds, coupled with the demonstrations that tCDK inhibitors display promising complementary activity to existing cancer therapeutics, has substantially boosted interest in the field, with several synergistic drug combinations showing potential to translate into clinical use in the near future.

REFERENCES

1. Fisher RP. Cdk7: a kinase at the core of transcription and in the crosshairs of cancer drug discovery. Transcription. 2019;10:47–56.
2. Sánsó M, Fisher RP. Pause, play, repeat. Transcription. 2013;4:146–52.
3. Bradner JE, Hnisz D, Young RA. Transcriptional addiction in cancer. Cell. 2017;168:629–43.
4. Heinlein CA, Chang C. Androgen receptor in prostate cancer. Endocr Rev. 2004;25:276–308.
5. Eck D, Geyer M. The RNA polymerase II carboxy-terminal domain (CTD) code. Chem Rev. 2013;113:8456–90.
6. Hsin JP, Manley JL. The RNA polymerase II CTD coordinates transcription and RNA processing. Genes Dev. 2012;26:2119–37.
7. Tsai TFF, Sigler PB. Structural basis of preinitiation complex assembly on human Pol II promoters. EMBO J. 2000;19:25–36.
8. Greber BJ, Toso DB, Fang J, Nogales E. The complete structure of the human TFIIH core complex. Elife. 2019;8:e44771.
9. Soutourina J. Transcription regulation by the Mediator complex. Nat Rev Mol Cell Biol. 2018;19:262–74.
10. Wong KH, Jin Y, Struhl K. TFIIH phosphorylation of the Pol II CTD stimulates mediator dissociation from the preinitiation complex and promoter escape. Mol Cell. 2014;54:601–12.
11. Luse DS. Promoter clearance by RNA polymerase II. Biochim Biophys Acta. 2013;1829:63–68.
12. Egloff S. Role of Ser7 phosphorylation of the CTD during transcription of snRNA genes. RNA Biol. 2012;9:1033–8.
13. Nilsson KA, Guo J, Turek ME, Brogie JE, Delaney E, Luse DS, et al. THZ1 reveals roles for Cdk7 in co-transcriptional capping and pausing. Mol Cell. 2015;59:576–87.
Greenleaf AL. Human CDK12 and CDK13, multi-tasking CTD kinases for the new millennium. Transcription. 2019;10:91–110.

Krajewska M, Dries R, Grassetti AV, Dust S, Gao Y, Huang H, et al. CDK12 loss in cancer cells affects DNA damage response genes through premature cleavage and polyadenylation. Nat Commun. 2019;10:1757.

Duberry SJ, Boutz PL, Sharp PA. CDK12 regulates DNA repair genes by suppressing intrinsic polyadenylation. Nature. 2018;564:141–45.

Jiang B, Gao Y, Che J, Liu W, Kalthauer IH, Dries R, et al. Discovery and resistance mechanism of a selective CDK12 degrader. Nat Chem Biol. 2021;17:675–83.

Tien JF, Mazloomian A, Cheng SW, Hughes CS, Chow CCT, Canapi LT, et al. Characterization of Human Cyclin-Dependent Kinase 12 (CDK12) and CDK13 Complexes in C-terminal domain phosphorylation, gene transcription, and RNA processing. Mol Cell Biol. 2015;35:928–38.

Kasten M, Giordano A. CdK10a, a CdC2-related kinase, associated with the Ets2 transcription factor and modulates its transcriptional activity. Oncogene. 2001;20:1832–8.

Guen VJ, Gambale C, Flajolet M, Unger S, Thollet A, Ferandin Y, et al. CDK10/cyclin M is a protein kinase that controls ETS2 degradation and is deficient in STAR syndrome. Proc Natl Acad Sci USA. 2013;10:19525–30.

Loyer P, Trembley JH,grenet JA, Busson A, Corlu A, Zhao W, et al. Characterization of cyclin L1 and L2 interactions with CDK11 and splicing factors: influence of cyclin L isoforms on splice site selection. J Biol Chem. 2008;283:7721–32.

Gómez-Escalona P, Ruiz de los Mozos L, Jáuregui M, Hlushy M, Ule J, Blazek D. CDK11 is required for transcription of replication-dependent histone genes. Nat Struct Mol Biol. 2020;27:500–10.

Tomlins SA, Rhodes DR, Perner S, Dhanasekaran SM, Mehra R, Sun XW, et al. Recurrent fusion of TMPRSS2 and ETS transcription factor genes in prostate cancer. Science. 2005;310:644–8.

Nam RK, Sugar L, Yang W, Srivastava S, Klotz LH, Yang YL, et al. Expression of the TMPRSS2:ERG fusion gene predicts cancer recurrence after surgery for localised prostate cancer. Br J Cancer. 2007;97:1690–9.

Pomerantz MM, Li F, Takeda DY, Lenci R, Chonkar A, Chabot M, et al. The androgen receptor cistrome is extensively reprogrammed in human prostate tumorigenesis. Nat Genet. 2015;47:1346–51.

West TA, Kiely BE, Stockler MR. Estimating scenarios for survival time in men starting systemic therapies for castration-resistant prostate cancer. JUrol. 2007;20:1832–8.

Tien JF, Mazloomian A, Cheng SW, Hughes CS, Chow CCT, Canapi LT, et al. Characterization of Human Cyclin-Dependent Kinase 12 (CDK12) and CDK13 Complexes in C-terminal domain phosphorylation, gene transcription, and RNA processing. Mol Cell Biol. 2015;35:928–38.
phosphorylation of STAT1 and STAT5 transactivation domains. Oncotarget. 2017;8:33779–95.
88. Kalan S, Armat R, Schachter MM, Kwiatkowski N, Abraham BJ, Liang Y, et al. Activation of the p53 transcriptional program sensitizes cancer cells to Cdk7 inhibitors. Cell Rep. 2017;21:467–81.
89. Henry SH, Johannessen L, Sawant P, Lefkovith A, Ke N, Dworakowski W, et al. 13P SY-S609, a highly potent and selective oral CDK7 inhibitor, exhibits robust antitumor activity in preclinical models of KRAS mutant cancers as a single agent and in combination with chemotherapy. Ann Oncol. 2021;32:5364–5375.
90. Zhang H, Panedy S, Travers M, Sun H, Morton G, Madzo J, et al. Targeting CDK9 reactivates epigenetically silenced genes in cancer. Cell. 2018;175:1244–1258. e26
91. Wei Y, Li C, Bian H, Qian W, Jin K, Xu T, et al. Targeting CDK7 suppresses super enhancer-linked inflammatory genes and alleviates CAR T cell-induced cytokine release syndrome. Mol Cancer. 2021;20:5.
92. McDermott MSJ, Sharko AC, Munie J, Kassler S, Melendez T, Lim CU, et al. CDK7 inhibition is effective in all the subtypes of breast cancer: determinants of response and synergy with EGFR inhibition. Cells. 2020;9:638.
93. McLaughlin RP, He J, Van Der Noord VE, Redel J, Fink A, Hung E, et al. A kinase inhibitor screen identifies a dual cdc7/CDK9 inhibitor to sensitize triple-negative breast cancer to EGFR-targeted therapy. Breast Cancer Res. 2019;21:77.
94. Sun B, Mason S, Wilson RC, Hazard SE, Wang Y, Fang R, et al. Inhibition of the transcriptional kinase CDK7 overcomes therapeutic resistance in HER2-positive breast cancers. Oncogene. 2020;39:50–63.
95. Phillips DC, Jin S, Gregory GP, Zhang Q, Xue J, Zhao X, et al. A novel CDK9 inhibitor increases the efficacy of venetoclax (ABT-199) in multiple models of hematologic malignancies. Leukemia. 2020;34:1646–57.
96. Luedtke DA, Su Y, Ma J, Li X, Buck SA, Edwards H, et al. Inhibition of CDK9 by voruciclib synergistically enhances cell death induced by the Bcl-2 selective inhibitor venetoclax in preclinical models of acute myeloid leukemia. Signal Transduct Target Ther. 2020;5:17.
97. Zhang Z, Peng H, Wang Y, Yin X, Ma P, Jing Y, et al. Preclinical efficacy and molecular mechanism of targeting CDK7-dependent transcriptional addiction in ovarian cancer. Mol Cancer Ther. 2017;16:1739–50.
98. Durbin AD, Zimmerman MW, Dharia NV, Abraham BJ, Iniguez AB, Weichert-Leahey N, et al. Selective gene dependencies in MYCN-amplified neuroblastoma include the core transcriptional regulatory circuitry. Nat Genet 2018;50:1240–5.
99. McLaughlin RP, He J, Van Der Noord VE, Redel J, Fink A, Hung E, et al. A kinase inhibitor screen identifies a dual cdc7/CDK9 inhibitor to sensitize triple-negative breast cancer to EGFR-targeted therapy. Breast Cancer Res. 2019;21:77.
100. McDermott MSJ, Sharko AC, Munie J, Kassler S, Melendez T, Lim CU, et al. CDK7 inhibition is effective in all the subtypes of breast cancer: determinants of response and synergy with EGFR inhibition. Cells. 2020;9:638.
101. Rusan M, Li K, Li Y, Christensen CL, Abraham BJ, Kwiatkowski N, et al. Suppression of adaptive responses to targeted cancer therapy by transcriptional repression. Cancer Discov. 2018;8:59–73.
102. Sun B, Mason S, Wilson RC, Hazard SE, Wang Y, Fang R, et al. Inhibition of the transcriptional kinase CDK7 overcomes therapeutic resistance in HER2-positive breast cancers. Oncogene. 2020;39:50–63.
103. Phillips DC, Jin S, Gregory GP, Zhang Q, Xue J, Zhao X, et al. A novel CDK9 inhibitor increases the efficacy of venetoclax (ABT-199) in multiple models of hematologic malignancies. Leukemia. 2020;34:1646–57.
104. Guarducci C, Nardone A, Feiglin A, Migliaccio I, Malorni L, Bonechi M, et al. Abstract PD7-12: Inhibition of CDK7 overcomes resistance to CDK4/6 inhibitors in hormone receptor positive breast cancer cells. In: Proceedings of the 2018 San Antonio Breast Cancer Symposium; 2018 Dec 4-8. AACR: San Antonio, TX. Philadelphia (PA), 2019, pp PD7–12.

ACKNOWLEDGEMENTS
This work was supported by the Medical Research Council Doctoral Training Partnership (TAC and KKG) (grant number MR/N014103/1) and the Imperial President’s PhD Scholarship (TAC).

AUTHOR CONTRIBUTIONS
TAC and KKG conceived the review, designed and produced illustrative material, and wrote the manuscript. AVC and CLB supervised and revised the manuscript. All authors approved the final version.

COMPETING INTERESTS
CLB has received research grant funding from Carrick Therapeutics. Other authors declare no potential competing interests.

ADDITIONAL INFORMATION
Correspondence and requests for materials should be addressed to Charlotte L. Bevan.

Reprints and permission information is available at http://www.nature.com/reprints

Publisher’s note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/.

© The Author(s) 2022