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REVIEW

The important role of the histone acetyltransferases p300/CBP in cancer and the promising anticancer effects of p300/CBP inhibitors

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Abstract Histone acetyltransferases p300 (E1A-associated protein p300) and CBP (CREB binding protein), collectively known as p300/CBP due to shared sequence and functional synergy, catalyze histone H3K27 acetylation and consequently induce gene transcription. p300/CBP over-expression or over-activity activates the transcription of oncogenes, leading to cancer cell growth, resistance to apoptosis, tumor initiation and development. The discovery of small molecule inhibitors targeting p300/CBP histone acetyltransferase activity, bromodomains, dual inhibitors of p300/CBP and BRD4 bromodomains, as well as proteolysis-targeted-chimaera p300/CBP protein degraders, marks significant progress in cancer therapeutics. These inhibitors and degraders induce histone H3K27 deacetylation, reduce oncogene expression and cancer cell proliferation, promote cancer cell death, and decrease tumor progression in mice. Furthermore, p300/CBP inhibitors and protein degraders have been demonstrated to exert synergy when in combination with conventional radiotherapy, chemotherapy and BRD4 inhibitors *in vitro* as well as in mice. Importantly, two p300/CBP bromodomain inhibitors, CCS1477 and FT-7051, as well as the dual p300/CBP and BRD4 bromodomain inhibitor NEO2734 have entered Phase I and IIa clinical trials in patients with advanced and refractory hematological malignancies or solid tumors. Taken together, the identification of p300/CBP as critical drivers of tumorigenesis and the development of p300/CBP inhibitors and proteolysis-targeted-chimaera protein degraders represent promising avenues for clinical translation of novel cancer therapeutics.

Keywords P300 · CBP · Transcription · Tumorigenesis · Small molecule inhibitors · Cancer treatment

Xin Wu and Xin Zhang made equal contributions to this work.

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Introduction

RNA polymerases II (RNA Pol II) catalyses gene transcription to generate message RNAs (mRNAs) (Girbig et al. 2022). Initiation of gene transcription involves RNA Pol II phosphorylation at Serine 5 of

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the carboxy-terminal domain (CTD); RNA Pol II phosphorylated at Serine 5 bind to target gene promoters, launching RNA synthesis from the transcription start site (initiation); and subsequently RNA Pol II phosphorylated at Serine 2 of the CTD traverses along exons and introns of the gene (elongation) up till the end of the last exon (Cramer 2019; Schier and Taatjes 2020).

Transcriptional enhancers are DNA segments bound by histones acetylated at H3 lysine 27 (H3K27). Enhancers amplify nearby gene transcription, irrespective of sense or antisense directions, since enhancers possess the ability to loop over considerable genomic distances to activate gene promoters (Pennacchio et al. 2013). Super-enhancers comprise enhancer clusters, predominantly concentrate at key cellular genes such as stem cell genes and oncogenes, and play critical roles in cell identify definition, oncogene transcription and over-expression (Chapuy et al. 2013; Hnisz et al. 2013; Loven et al. 2013; Wong et al. 2019).

E1A-associated protein p300 (p300) and CREB binding protein (CBP) are histone acetyltransferases that catalyse the acetylation of histone proteins. When histone H3 is acetylated by p300 and CBP at K27, the chromatin structure becomes more accessible, facilitating transcriptional activation at gene promoters, enhancers and super-enhancers (Narita et al. 2021; Pasini et al. 2010; Raisner et al. 2018; Weinert et al. 2018). Owing to their substantial similarity, p300 and CBP are often collectively referred to as p300/CBP (Ramos et al. 2010; Zeng et al. 2008). Initially recognized as tumor suppressors in certain cancers, such acute lymphoblastic leukemia due to *EP300* and *CREBBP* gene rearrangement with the *ZNF384* gene, generation of fusion proteins between p300/CBP and and loss of p300/CBP function (Qian et al. 2017), p300/CBP have more recently been elucidated as crucial transcriptional activators of pivotal oncogenes (Asante et al. 2023; Hogg et al. 2021; Narita et al. 2021).

Developing drugs for epigenetic modulators has been challenging due to the complex and reversible nature of epigenetic regulation, as well as the difficulty in achieving selectivity. Epigenetic regulators often share highly conserved protein domains, making it difficult to design inhibitors that are specific enough to avoid off-target effects. For example, DNA methyltransferase and histone deacetylase inhibitors reactivate tumor suppressor gene expression by reversing abnormal DNA methylation and altering chromatin structure, respectively. However, their clinical applications have been limited (Falkenberg and Johnstone 2014; Pechalrieu et al. 2017). Importantly, small molecule p300/CBP inhibitors have recently been discovered, the anticancer efficacy of the p300/CBP inhibitors has been demonstrated *in vitro* and in mouse models, and three of them, including CCS147, FT-7051 and NEO2734, have entered clinical trials in cancer patients (Armstrong et al. 2021; Crabb et al. 2021; He et al. 2021; Picaud et al. 2015).

Distinct from reported review articles, here we aim to provide the most up-to-date and most comprehensive analysis of the role of histone acetyltransferases p300/CBP in cancer development, the advancements in p300/CBP inhibitor and protein degrader development, and preclinical and clinical evaluation of these novel anticancer agents.

p300/CBP induce histone H3K27 acetylation and activate gene transcription

The p300/CBP proteins induce histone acetylation due to their histone acetyltransferase (HAT) domain (Bannister and Kouzarides 1996; Ogryzko et al. 1996). p300/CBP proteins comprise the HAT domain, bromodomain, KIX domain, cysteine/histidine-rich (CH) domains, ZZ and the nuclear receptor interaction domains. Notably, p300 and CBP HAT domain mutations result in varying degrees of reduction in acetyltransferase activity, suggesting subtle distinctions between the two proteins (Bordoli et al. 2001).

Inhibition of the p300/CBP HAT domain results in H3K27 deacetylation and transcriptional suppression, akin to the effects observed after p300/CBP knockdown (Yokomizo et al. 2011), while p300/CBP bromodomain suppression also results in H3K27 deacetylation and a decrease in gene expression (Raisner et al. 2018). The observations indicate that, in addition to the HAT domain, the bromodomain is also essential for p300/CBP-dependent H3K27 acetylation and gene transcription.

p300/CBP interact with transcription factors including TFAP2β to induce histone H3K27 acetylation, resulting in the recruitment of BRD4 and other transcription factors and the formation of enhancers and super-enhancers at oncogene and cell identity

gene loci (Chan et al. 2019; Durbin et al. 2022; Narita et al. 2021; Ormsbee Golden et al. 2024; Wong et al. 2019; Wu et al. 2018). BRD4 and transcription factors then recruit positive transcription elongation factor b (P-TEFb), Mediator and RNA Polymerase II at target gene super-enhancers, enhancers and promoters, leading to oncogene transcriptional initiation, RNA Polymerase II release from pause regions, transcriptional elongation and oncogene over-expression (Narita et al. 2021; Ormsbee Golden et al. 2024) (Fig. 1). Moreover, p300/CBP can independently recruit RNA Polymerase II to augment transcription factor IID at oncogene promoters and enhancers to induce oncogene transcription (Narita et al. 2021).

p300/CBP also regulate gene expression through acetylating transcription factors. p300/CBP bind to and acetylate c-Myc at Myc-responsive elements, leading to Myc protein de-ubiquitination and stabilization and Myc target gene transcription (Hurd et al. 2023; Vervoorts et al. 2003). p300/CBP interact with NF-κB at NF-κB target gene promoters and enhancers, acetylate the NF-κB heterodimer component RelA/p65, and activate target gene transcription and expression (Hoberg et al. 2006; Mukherjee et al. 2013). p300/CBP also directly interact with the negative regulatory domain of c-Myb oncoprotein and acetylate c-Myb, and the acetylation considerably enhances the trans-activating capacity of c-Myb (Sano and Ishii 2001; Tomita et al. 2000). In addition, p300 binds and acetylates GATA-3, a proto-oncogene for T-cell lymphoproliferative neoplasms, and the acetylation is required for optimal GATA-3 target gene transcription (Geng et al. 2022).

p300/CBP induce tumor initiation and progression

Melanoma p300/CBP facilitate transcriptional landscape reprogramming during tumorigenesis. An analysis of The Cancer Genome Atlas datasets reveals *EP300* gene gain in approximately 25% of acral melanoma compared with cutaneous melanoma (10%) and other cancers (0–10%). In melanoma cells with *EP300* gene gain, inhibition of p300 reduces oncogenic *TGFB1*, *AXL*, *WNT5A* and *MITF* gene expression and cell proliferation (Shi et al. 2022).

Hepatocellular carcinoma In a quarter of hepatocellular carcinomas, *EP300* is either amplified or gained, with its over-expression predicting poor patient prognosis (Tsang et al. 2019). p300 plays a pivotal role in super-enhancer reprogramming in the course of liver carcinogenesis, promoting the transcription of *YAP1*, *E2F2* and *MYC,* key super-enhancer-regulated carcinogenic genes. Consequently, p300 promotes liver cancer cell survival and is required for liver tumorigenesis in mouse models (Tsang et al. 2019) (Fig. 2).

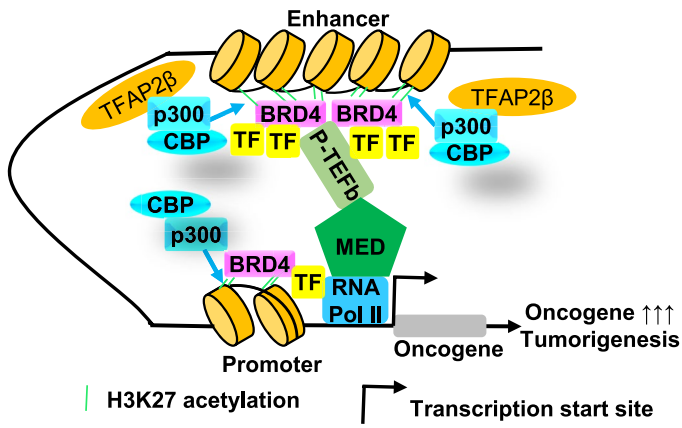


Fig. 1 p300/CBP induce histone H3 lysine 27 acetylation and oncogene transcription. p300/CBP interact with transcription factors including TFAP2β to induce histone H3 lysine 27 (H3K27) acetylation at oncogene promoters and enhancers, leading to BRD4, transcription factor, positive transcription elongation factor b (P-TEFb), Mediator (MED), and RNA Polymerase II (RNA Pol II) recruitment, oncogene transcription and tumorigenesis

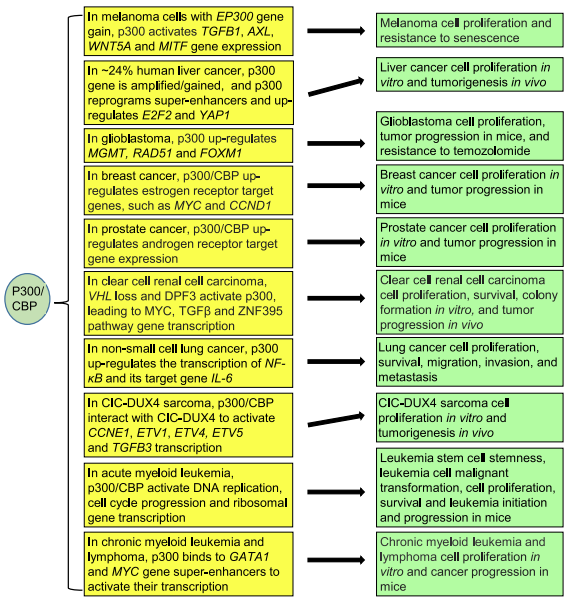


Fig. 2 p300/CBP activate oncogene expression and induce cancer cell proliferation and survival *in vitro* and tumor progression *in vivo*

Glioblastoma The chromatin-modifying complex protein RBBP4 interacts with p300 to induce histone acetylation at promoters and enhancers of target genes, such as *MGMT* and *RAD51*, leading to their over-expression in glioblastoma cells. p300 thereby stimulates glioblastoma cell proliferation and resistance to anticancer agents (Chen et al. 2018; Kitange et al. 2016). In glioma stem cells, CBP is recruited to *FOXM1* gene loci by SATB2, resulting in *FOXM1* up-regulation, glioma stem cell proliferation *in vitro* and glioblastoma growth *in vivo* (Tao et al. 2020) (Fig. 2).

Breast cancer In breast cancer cells, interferon γ recruits p300 to target gene enhancers, leading to chromatin remodelling, histone H3K27 acetylation, RNA Pol II recruitment and interferon γ target gene transcription (Hogg et al. 2022). The LIM protein Ajuba recruits p300/CBP to estrogen receptor α to increase its DNA-binding and transcriptional activities, leading to aberrant up-regulation of estrogen receptor α target genes, including *CCND1* and *MYC*, and breast cancer cell multiplication and tumor growth in cell culture and in mice (Waddell et al. 2021; Xu et al. 2019) (Fig. 2).

Prostate cancer Analysis of RNA sequencing data obtained from prostate cancer and paired normal tissues reveals p300 and CBP up-regulation in tumors which is associated with androgen receptor up-regulation and the androgen receptor-mediated gene transcription profile (Helminen et al. 2024; Welti et al. 2021). In castration-resistant prostate cancer cells, p300 and CBP bind to androgen receptor-binding sites at gene enhancers to augment androgen receptor-mediated gene transcription, ultimately promoting cancer cell division and tumor progression in mice (Welti et al. 2021) (Fig. 2).

Kidney cancer In clear cell renal cell carcinomas, the SWI/SNF chromatin remodeling complex protein DPF3 interacts with SNIP1 to release the repressive effect of SNIP1 on p300, and deficiency of Von Hippel-Lindau, a tumor suppressor, triggers p300 protein binding at super-enhancers and enhancers of several oncogenic genes (Cui et al. 2022; Yao et al. 2017). p300 protein then induces histone H3K27 acetylation, the over-expression of MYC, ZNF395 and TGF-β pathway genes, clear cell renal cell carcinoma cell multiplication, resistance to cell death, and invasion, as well as tumor growth in mice (Cui et al. 2022; Yao et al. 2017) (Fig. 2).

Lung cancer RNA sequencing analysis of *CBP*-deficient lung cancer cells reveals that p300 substantially augments *MYC* gene expression, and is indispensable in *CBP*-defective lung cancer cell multiplication, cell cycle progression and survival in vitro and tumor progression *in vivo* (Ogiwara et al. 2016). In addition, p300 increases *NF-κB* gene transcription and subsequently NF-κB target gene *IL-6* expression, leading to increased expression of mesenchymal marker genes and decreased expression of epithelial marker genes, promoting non-small cell lung cancer cell survival, proliferation, and metastasis (Ansari et al. 2023; Wang et al. 2018b) (Fig. 2).

Sarcoma CIC-DUX4 sarcoma is caused by the fusion of the transcription factor CIC to the C-terminal domain of the transcription factor DUX4. p300/CBP interact with CIC-DUX4 to induce histone H3K27 acetylation, activate the transcription of CIC-DUX4 target genes including *CCNE1*, *ETV1*, *ETV4, ETV5* and *TGFB3*, and result in sarcoma cell division

in vitro and tumorigenesis in mice (Bosnakovski et al. 2021) (Fig. 2).

Leukemia and lymphoma In acute myeloid leukemia, p300/CBP play a crucial role in regulating ribosomal gene and DNA replication as well as cell cycle gene transcription, and p300/CBP are indispensable in acute myeloid leukemia malignant transformation, cell proliferation, leukemia induction and maintenance (Diesch et al. 2021; Giotopoulos et al. 2016; van Gils et al. 2021). In addition, p300 is considerably over-expressed in acute myeloid leukemia tissues, is recruited to oncogene enhancer regions in leukemia stem cells, and is required for the transcription and over-expression of key oncogenes in leukemia stem cells (Pan et al. 2023). p300 knockdown reduces H3K27 acetylation at enhancers and the expression of enhancer–associated oncogenes, and induces leukemia stem cell differentiation (Pan et al. 2023) (Fig. 2).

In chronic myeloid leukemia as well as lymphoma, p300 binds at the *MYC* and *GATA1* super-enhancers, and suppression of p300/CBP disrupts the expression of *GATA1* and *MYC* oncogenes, leading to reduction in cell cycle progression and cell proliferation (Garcia-Carpizo et al. 2018). In anaplastic large cell lymphoma and Hodgkin lymphoma, p300 activates the expression of oncogenic MYC/IRF4 network, surface receptor CD30 and immune checkpoint PD-L1 genes, by binding to their gene enhancers. Suppression of p300 with HAT or bromodomain inhibitors leads to inhibition of PD-L1-mediated tumor immune escape, anaplastic large cell lymphoma and Hodgkin lymphoma cell death in cell culture and tumor progression arrest in mice xenografted with lymphoma cells (Wei et al. 2023) (Fig. 2).

Small molecule compound inhibitors of p300/CBP

There are four main classes of p300/CBP inhibitors: p300/CBP HAT inhibitors, p300/CBP bromodomain inhibitors, dual p300/CBP and BRD4 bromodomain inhibitors, and proteolysis-targeted-chimaera (PROTAC) p300/CBP degraders. While early research focuses on p300/CBP HAT or bromodomain inhibitor discovery, dual p300/CBP and BRD4 bromodomain inhibitors and PROTAC p300/CBP degraders are becoming increasingly more attractive cancer therapy agents. Major p300/CBP inhibitors of all the four classes have been summarized below.

p300/CBP HAT inhibitors

Early weak p300/CBP HAT inhibitors

Garcinol from garcinia and anacardic acid from cashew nutshell are natural product p300/CBP HAT inhibitors, and weakly suppress HAT-dependent transcription from a chromatin template at μM concentrations (Balasubramanyam et al. 2004, 2003). Lys-CoA was synthesized 20 years ago and found to function as a HAT inhibitor against p300 with a half-maximal inhibitory concentration (IC_{50}) value of 500 nM (Lau et al. 2000).

CCT077791, CCT077792 and "compound 21"

A FlashPlate high-throughput screen has identified the isothiazolone-based small molecules CCT077791 and CCT077792 as p300 HAT inhibitors which reduce histone acetylation and cancer cell proliferation at low μM and sub-μM concentrations respectively (Stimson et al. 2005) (Table 1). Through medicinal chemistry modification, the p300 HAT inhibitor "compound 21" has been synthesized and suppresses HAT at 11 nM for IC_{50} (Ji et al. 2021).

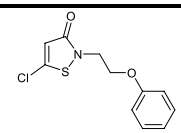
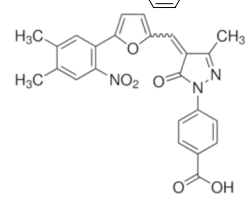
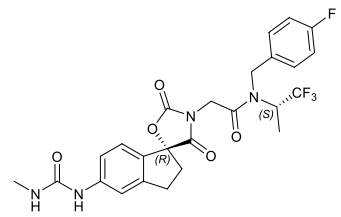
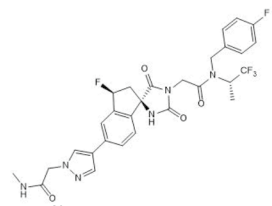
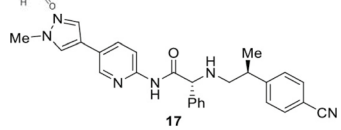
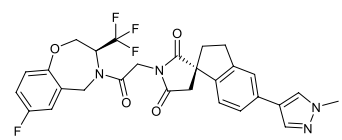
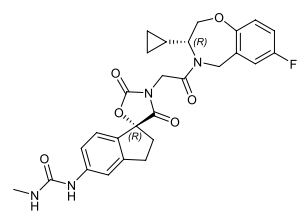
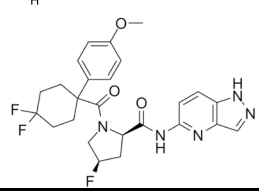
C646

Structure-based in silico screens have identified the drug-like small molecule compounds C646 and A-485 as highly selective p300/CBP HAT inhibitors (Bowers et al. 2010; Lasko et al. 2017). Experiments with p300 HAT mutants and C646 derivatives confirm the specificity of C646 in interacting with p300 and inducing histone deacetylation with an inhibitory constant concentration of 400 nM (Bowers et al. 2010) (Table 1).

A-485 and iP300w

The considerably more potent spirocyclic HAT inhibitor A-485 preferentially deacetylates histone H3K27 at enhancers across the genome, represses p300- and CBP-induced histone acetylation with IC_{50} values of 9.8 nM and 2.6 nM respectively, reduces enhancer-associated androgen receptor-stimulated

Table 1 p300/CBP HAT inhibitors reduce oncogene expression and exert anticancer effects *in vitro* and *in vivo*

Inhibitors	Structures	Anticancer effects *in vitro* and *in vivo*	References
CCT077792		Suppresses histone H3 and H4 acetylation and colon cancer cell proliferation at sub μM concentrations.	(Stimson et al. 2005)
C646		Suppresses p300 (inhibitory constant of 0.4 μM); represses DNA replication, DNA repair, cell cycle progression and mitosis gene expression; and reduces lymphoma, leukemia and pancreatic cancer cell proliferation, survival and *in vivo* progression.	(Bowers et al. 2010; Giotopoulos et al. 2016; Oike et al. 2014)
A-485		Suppresses p300 and CBP with IC_{50} values of 9.8 nM and 2.6 nM; represses *MYC* and androgen receptor-mediated gene expression; and reduces prostate cancer, NUT midline carcinoma, lymphoma, leukaemia and myeloma cell proliferation *in vitro* and tumor progression in mice.	(Lasko et al. 2017) (Pan et al. 2023; Waddell et al. 2021; Wei et al. 2023)
iP300w		Suppresses p300 with an IC_{50} value of 4.1 nM, represses DUX4 and CIC-DUX4 target gene expression, and reduces sarcoma cell proliferation *in vitro* and tumor progression in mice.	(Bosnakovski et al. 2019; Bosnakovski et al. 2021)
CPI-1612		Suppresses p300 with an IC_{50} value of 8.1 nM, represses *hERG*, *MYC* and *RAD51* expression, and reduces B-cell lymphoma and glioblastoma cell viability and tumor progression in mice.	(Mladek et al. 2022; Wilson et al. 2020)
B026		Suppresses p300 and CBP with IC_{50} values of 1.8 nM and 9.5nM, represses *MYC* transcription, and reduces acute myeloid leukemia cell proliferation *in vitro* and leukemia progression in mice.	(Yang et al. 2020)
B029-2		Suppresses p300 and CBP with IC_{50} values of 0.5 nM and 11 nM, represses metabolism and nucleotide synthesis gene expression, and reduces hepatocellular carcinoma cell proliferation *in vitro* and tumor progression in mice.	(Cai et al. 2021)
DS-9300		Suppresses CBP with an IC_{50} value of 22 nM, and reduces prostate cancer cell proliferation and survival *in vitro* and blocks prostate cancer progression in mice.	(Kanada et al. 2023)

gene transcription but shows no effects on genes negatively regulated by androgen receptor in prostate cancer cells (Lasko et al. 2017) (Table 1). iP300w, another spirocyclic HAT inhibitor with A-485-related structure, has been found to suppress histone H3 acetylation at 4.1 nM for the IC_{50}. Through interacting with the transcription factor DUX4 and CIC-DUX4, p300/CBP induce histone H3K27 acetylation and the transcription of DUX4 target genes such as *LEUTX* and CIC-DUX4 target genes such as *CCNE1* and *ETV1*, and iP300w reduces H3K27 acetylation and blocks the transcription of DUX4 and CIC-DUX4 target genes *in vitro* and in a mouse model (Bosnakovski et al. 2019; Bosnakovski et al. 2021) (Table 1.).

CPI-1612

The p300/CBP HAT inhibitor CPI-1612 was developed through medicinal chemistry modifications to a "hit" p300/CBP HAT inhibitor identified in a high-throughput compound library screen. CPI-1612 reduces H3K27 acetylation *in vitro* and in a mouse model, suppresses the HAT activity of p300 at 8.1 nM for the IC_{50} in scintillation proximity assays; and reduces the expression of p300/CBP target genes such as *hERG, MYC* and *RAD51* (Mladek et al. 2022; Wilson et al. 2020) (Table 1). Interestingly, in a recent study comparing the HAT inhibitory activity of A-485, iP300w and CPI-1612, at the presence of 50 nM acetyl-CoA, CPI-1612 has been identified as the most potent p300/CBP HAT inhibitor (IC_{50} = 10.7 nM), followed by iP300w (IC_{50} = 15.8 nM) and A-485 (IC_{50} = 44.8 nM) (Crawford et al. 2023).

B026 and B029-2

In silico screen and further optimization have identified the drug-like small molecule compound B026 as a highly selective p300/CBP HAT inhibitor with an IC_{50} of 1.8 nM against p300 and 9.5 nM against CBP (Yang et al. 2020) (Table 1). Further optimization of B026 has led to the discovery of B029-2, which exhibits more potent inhibitory effect against the HAT activity of p300 and CBP at 0.52 nM and and 11 nM for the IC_{50} respectively. Treatment with B029-2 disrupts metabolic reprogramming and suppresses nucleotide synthesis and glycolysis by decreasing H3K27 acetylation at the nucleotide synthesis and amino acid metabolism enzyme gene promoters (Cai et al. 2021) (Table 1).

DS-9300

The highly potent and selective p300/CBP HAT inhibitor DS-9300 has been developed through structure-based drug design. DS-9300 represses HAT activity of CBP with an IC_{50} value of 22 nM, reduces histone H3K27 acetylation, and show excellent pharmacokinetic properties (Kanada et al. 2023) (Table 1).

p300/CBP bromodomain inhibitors

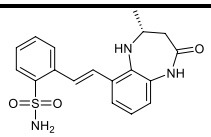
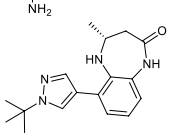
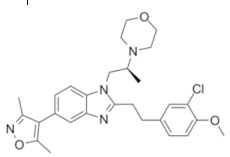
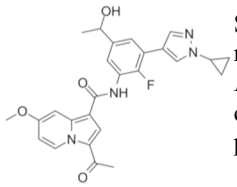
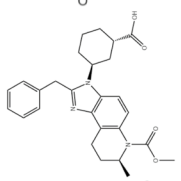
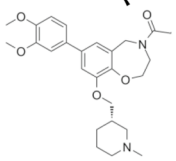
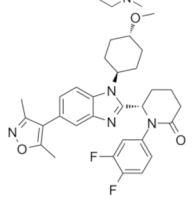
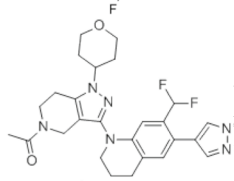
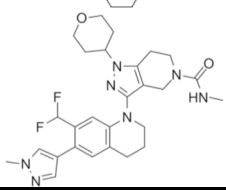
CPI644 and CPI703

Screen of a library of ~1200 compounds with differential scanning fluorimetry has identified CPI644 and CPI703 as p300/CBP bromodomain inhibitors with IC_{50} values of 0.18 μm and 0.47 μm for suppressing CBP bromodomain binding in a cell-free system respectively and cellular EC_{50} of 0.53 μm and 2.1 μm for suppressing CBP bromodomain binding in cells respectively (Ghosh et al. 2016). Treatment with CPI644 or CPI703 results in a reduction in H3K27 acetylation, the transcription of several genes, including *FOXP3, LAG3*, *CTLA4*, and *PDCD1* (PD-1), and regulatory T cell differentiation (Ghosh et al. 2016) (Table 2).

CBP30, Y08284 and FT-6876

The p300/CBP bromodomain inhibitors CBP30 and Y08284 have been developed from a series of 5-isoxazolyl-benzimidazoles and 1-(indolizin-3-yl) ethan-1-one compounds respectively, show high potency and selectivity, and exhibit nanomolar affinity for p300/CBP in cells (Hay et al. 2014; Xiang et al. 2022). The dissociation constant (K_D) values of CBP30 and Y08284, calculated from the steady-state dose–response curve, were 47 nM for p300 and 38 nM for CBP by CBP30 and 58 nM for CBP by Y08284. CBP30 reduces IL-17A transcription and expression in immune cells (Hammitzsch et al. 2015) and Y08284 decreases androgen receptor target gene and *MYC* gene expression in prostate cancer cells (Xiang et al. 2022) (Table 2). Modification of CBP30 results in the development of FT-6876, a potent inhibitor of acetylated histone H3 binding to the bromodomain of p300 and CBP, with IC_{50} values of 2 nM and 5 nM respectively. Treatment with FT-6876 decreases

Table 2 p300/CBP bromodomain inhibitors reduce oncogene expression and exert anticancer effects

Inhibitors	Structures	Anticancer effects *in vitro* and *in vivo*	References
CPI644		Suppresses CBP with an IC_{50} value of 180 nM and a cellular EC_{50} value of 530 nM, represses *FOXP3* expression, and induces breast cancer and prostate cancer cell growth inhibition.	(Garcia-Carpizo et al. 2019; Ghosh et al. 2016)
CPI703		Suppresses CBP with an IC_{50} value of 470 nM; represses *FOXP3, LAG3*, *CTLA4* and *PDCD1* (PD-1) expression in regulatory T cells; and reduces their differentiation.	(Garcia-Carpizo et al. 2019; Ghosh et al. 2016)
CBP30		Suppresses p300 and CBP with dissociation constant (K_D) values of 47 nM and 38 nM; represses *IL-17A, MYC, SOX2* and *GATA1* gene expression; and induces breast, prostate and lung cancer cell growth inhibition.	(Hammitzsch et al. 2015; Hay et al. 2014; Kim et al. 2017)
Y08284		Suppresses CBP with a K_D value of 58 nM, represses androgen receptor target gene and *MYC* gene expression, and reduces prostate cancer cell proliferation *in vitro* and tumor progression in mice.	(Xiang et al. 2022)
FT-6876		Suppresses p300 and CBP with IC_{50} values of 2 nM and 5 nM, represses the transcription of androgen and estrogen receptor target genes, and reduces breast cancer cell proliferation *in vitro* and tumor progression in mice.	(Caligiuri et al. 2023)
I-CBP112		Suppresses p300 and CBP with K_D of 167 and 151 nM, represses key immune response and ATP-binding cassette transporter gene expression, reduces leukemogenesis in mice and sensitizes cancer cells to chemotherapy.	(Picaud et al. 2015; Strachowska et al. 2021)
CCS1477		Suppresses p300 and CBP with K_D values of 1.3 nM and 1.7 nM; represses *MYB*, *MYC* and androgen receptor expression and signalling; and reduces prostate cancer, acute myeloid leukemia, myeloma and NUT midline carcinoma progression in mouse models.	(Nicosia et al. 2023; Welti et al. 2021)
GNE-049		Suppresses p300 and CBP with IC_{50} of 2.3 nM and 1.1 nM, represses androgen receptor and its target gene expression, and reduces castration-resistant prostate cancer cell proliferation *in vitro* and tumor progression in mice.	(Jin et al. 2017; Waddell et al. 2021)
GNE-781		Suppresses p300 and CBP with IC_{50} values of 1.2 nM and 0.94 nM, represses *MYC* and *FOXP3* expression, and reduces acute myeloid leukemia and NUT midline carcinoma cell proliferation *in vitro* and acute myeloid leukemia progression in mice.	(Romero et al. 2017)

H3K27 acetylation and transcription of androgen receptor and estrogen receptor target genes (Caligiuri et al. 2023) (Table 2).

I-CBP112 and CCS1477

I-CBP112 and CCS1477 have been developed as specific and potent acetylated lysine competitive CBP/p300 bromodomain protein–protein interaction inhibitors. I-CBP112 shows K_D values of 167 nM and 151 nM for p300 and CBP respectively, and decreases the expression of key immune response genes including *FCGR1B* (CD64) and *TNFSF13B* (Picaud et al. 2015). CCS1477 exhibits K_D values of 1.3 nM and 1.7 nM for p300 and CBP respectively. CCS1477 decreases *MYC* and androgen receptor levels in prostate cancer cells, represses androgen receptor expression and signalling in mice with castration-resistant prostate cancer patient-derived xenografts and in patients in a clinical trial (Welti et al. 2021) (Table 2).

GNE-049 and GNE-781

Structure-based design and synthesis have resulted in the p300/CBP bromodomain inhibitor GNE-049 with an IC_{50} of 2.3 nM for p300 and IC_{50} of 1.1 nM for CBP bromodomains in a bromodomain-binding assay, and GNE-049 suppresses androgen receptor and its target gene expression (Jin et al. 2017). GNE-781, a structurally similar CBP/p300 bromodomain inhibitor, suppresses p300 and CBP at 1.2 nM and 0.94 nM for the IC_{50}, reduces histone acetylation, and suppresses *MYC* and *OXP3* gene expression (Romero et al. 2017) (Table 2).

Dual p300/CBP and BRD4 bromodomain inhibitors

Dual p300/CBP and BRD4 bromodomain inhibitors, NEO2734 and NEO1132, have been discovered through compound screening and synthesis to co-target bromodomains of p300/CBP and BRD4 (Giles et al. 2018). NEO2734 binds to p300/CBP and BRD4 with K_D values of 31, 19 and 6 nM for p300, CBP and BRD4 respectively. On the other hand, NEO1132 shows K_D values of 80, 61 and 63 nM for p300, CBP and BRD4 respectively (Spriano et al. 2020). NEO2734 downregulates the expression of oncogenic genes including *MYC, BCL2* and *ASB2* in lymphoma cells and *CDCP1* in castrate-resistant prostate cancer cells (Ji et al. 2022; Spriano et al. 2020) (Table 3).

CN470 is another dual p300/CBP and BRD4 bromodomain inhibitor. CN470 binds to the bromodomains of p300, CBP and BRD4 with K_D values of 32, 20 and 23 nM, respectively; and treatment with CN470 decreases *MYC*, *CDK6* and *BCL2* mRNA expression in acute lymphoblastic leukemia cells (Imayoshi et al. 2022) (Table 3).

Proteolysis-targeted-chimaera (PROTAC) p300/CBP protein degraders

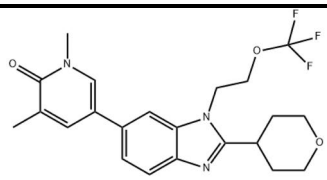
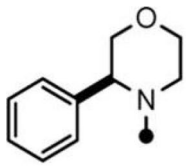
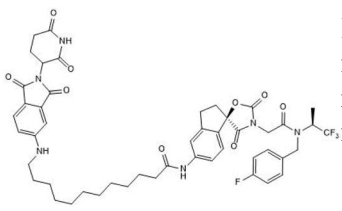
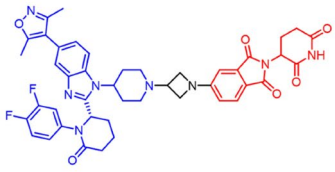
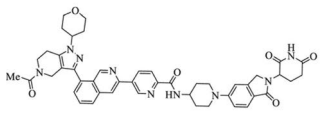
Three potent small molecule PROTAC degraders have recently been developed to target p300/CBP proteins for ubiquitination and degradation. Based on the p300/CBP HAT inhibitor A485 and the bromodomain inhibitor CCS1477, PROTACs JQAD1 and QC-182 have been designed and shown to bind to p300/CBP proteins and target them for ubiquitination and degradation with half-maximal degradation (DC_{50}) values of 31.6 nM for JQAD1 and 93 nM for QC-182 respectively in cancer cells (Chang et al. 2024; Durbin et al. 2022). JQAD1 and QC-182 decrease histone acetylation at H3K27 at the enhancers of core regulatory circuitry genes and reduce the transcription and expression of p300/CBP target oncogenes including epithelial-mesenchymal transition pathway-related genes *COL3A1* and *IGFBP3* (Chang et al. 2024; Durbin et al. 2022) (Table 3). Another potent PROTAC p300/CBP degrader, JET-209, shows a DC_{50} value of 0.2 nM for p300 and 0.05 nM for CBP and a maximum degradation value of > 95% for both proteins in cancer cells (Thomas et al. 2023) (Table 3).

p300/CBP inhibitors show promising anticancer effects *in vitro* and *in vivo*

p300/CBP HAT inhibitors as anticancer agents

C646, a p300/CBP HAT inhibitor, suppresses the expression of oncogenic genes important for DNA repair, cell cycle transition and mitosis such as *MYC*, *CCNB1* and *CDK1*; induces lymphoma, acute myeloid leukemia and pancreatic cancer cell cycle blockade and apoptosis; and represses leukemia and pancreatic cancer progression in mouse models (Giotopoulos et al. 2016; Ogiwara et al. 2016; Ono et al. 2021) (Table 1) (Fig. 3). In non-small cell lung cancer, C646 increases the hyperploid

Table 3 Dual p300/CBP and BRD4 bromodomain inhibitors and PROTAC p300/CBP protein degraders reduce oncogene expression and exert anticancer effects

Inhibitors	Structures	Bromodomain inhibition or p300/CBP protein degradation and anticancer effects	References
NEO2734		Suppresses p300 and CBP with K_D values of 31 nM and 19 nM; represses the transcription of oncogenic *MYC, BCL2*, *ASB2* and *CDCP1*; and reduces lymphoma, acute myeloid leukemia and prostate cancer cell proliferation *in vitro* and tumor progression in mice.	(Ji et al. 2022; Spriano et al. 2020; van Gils et al. 2021)
CN470		Suppresses p300, CBP and BRD4 with K_D values of 32, 20 and 23 nM respectively; represses *MYC*, *CDK6* and *BCL2* expression; and reduces acute lymphoblastic leukemia cell proliferation *in vitro* and cancer progression in mice.	(Imayoshi et al. 2022)
JQAD1		Induces p300 protein degradation with a half-maximal degradation (DC_{50}) value of 31.6nM, represses *MYCN* gene transcription, induces neuroblastoma cell apoptosis *in vitro*, and suppresses tumor progression in mice.	(Durbin et al. 2022)
QC-182		Induces p300/CBP protein degradation with a DC_{50} value of 93 nM, represses epithelial-mesenchymal transition pathway gene transcription, and reduces hepatocellular carcinoma cell proliferation and tumor progression in mice.	(Chang et al. 2024)
JET-209		Induces p300 and CBP protein degradation with DC_{50} values of 0.2 nM for p300 and 0.05 nM for CBP, reduces acute lymphoblastic leukemia cell proliferation *in vitro*, and suppresses leukemia progression in mice.	(Thomas et al. 2023)

cell population and suppresses CHK1 phosphorylation after radiation therapy, thereby enhancing cancer cell sensitivity to radiotherapy treatment and enhance radiotherapy-mediated mitotic catastrophe.

(Oike et al. 2014). Additionally, p300/CBP interact with MLL1 to suppress cancer cell response to EZH inhibitors, while C646 blocks EZH inhibitor-mediated histone H3K27ac accumulation (Huang et al. 2018).

A-485, a p300/CBP HAT inhibitor, displays considerable anticancer effects for prostate cancer, multiple myeloma, acute myeloid leukaemia, lymphoma, breast cancer and NUT midline carcinoma. In myeloma, acute myeloid leukemia and lymphoma cells, treatment with A-485 disrupts leukemia stem cell enhancer regulatory axis, suppresses PD-L1-mediated cancer cell immune escape, reduces leukemia stem cell self-renewal, and exerts potent anticancer effects against leukaemia, lymphoma and multiple myeloma *in vitro* and in mice (Pan et al. 2023; Wei et al. 2023). In melanoma, breast and prostate cancer cells, treatment with A-485 reduces histone H3

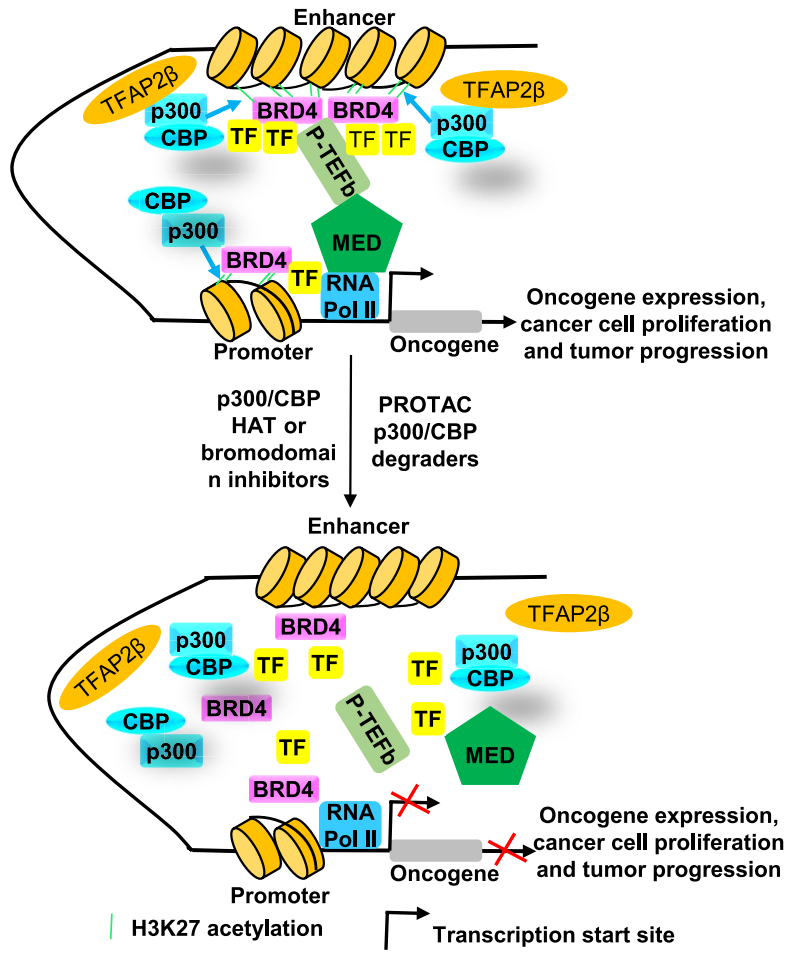


Fig. 3 p300/CBP inhibitors and protein degraders suppress oncogene transcription, expression, cancer cell proliferation and tumor progression. p300/CBP interact with transcription factors including TFAP2β to induce histone H3 lysine 27 (H3K27) acetylation, leading to BRD4, transcription factors (TF), positive transcription elongation factor b (P-TEFb), Mediator (MED), and RNA Polymerase II (RNA Pol II) recruitment, oncogene transcriptional activation, over-expression, cancer cell proliferation and tumor progression. Treatment with p300/CBP HAT inhibitors, bromodomain inhibitors or proteolysis-targeted-chimaera (PROTAC) protein degraders blocks the effects

acetylation and represses *MITF* and its downstream target gene expression in melanoma cells, *MYC* and *CCND1* gene expression in breast cancer cells, and androgen receptor expression in prostate cancer cells, resulting in melanoma, breast and prostate cancer cell senescence and growth inhibition (Lasko et al. 2017; Waddell et al. 2021; Wang et al. 2018a). In NUT midline carcinoma cells, epigenetic compound library screen discovers A-485 as one of the most effective anticancer agents against the disease. A-485 represses the expression of important oncogenes including *MYC*, *CCAT1* and *TP63*, triggers squamous differentiation, cell cycle arrest and programmed cell death. A-485 and BRD4 inhibitor combination therapy co-operatively induces NUT midline carcinoma cell apoptosis (Zhang et al. 2020). Additionally, treatment with GSK-J4, an inhibitor of the epigenetic regulator KDM6, and A-485 co-operatively down-regulate the transcription and expression of key oncogenic genes and leads to multiple myeloma cell apoptosis (Hogg et al. 2021) (Table 1).

In CIC-DUX4 sarcoma, CIC-DUX4 interacts with p300/CBP to activate its target gene expression and thereby drives tumorigenesis. Treatment with the p300/CBP HAT inhibitor iP300w, which shows a chemical structure similar to A-485, reverses CIC-DUX4 and p300/CBP-mediated gene transcription, induces sarcoma cell cycle arrest, substantially more effective than A-485, and suppresses sarcoma tumor growth in a mouse model (Bosnakovski et al. 2021) (Table 1).

The p300/CBP HAT inhibitor CPI-1612 reduces the expression of p300/CBP target genes such as *hERG*, *MYC* and *RAD51*; reduces B-cell lymphoma and glioblastoma cell viability; and represses tumor progression in mice (Mladek et al. 2022; Wilson et al. 2020). In addition, CPI-1612 and the chemotherapy agent temozolomide synergistically induce

glioblastoma cell apoptosis (Mladek et al. 2022) (Table 1).

The p300/CBP HAT inhibitor B026 reduces acute myeloid leukemia, lymphoma and prostate cancer cell proliferation partly through repressing *MYC* gene transcription, and suppresses acute myeloid leukemia progression in a mouse model (Yang et al. 2020). Treatment with B029-2, which exhibits a chemical structure similar to B026, reduces H3K27 acetylation and disrupts metabolic reprogramming and nucleotide synthesis by reducing the transcription of metabolism and nucleotide synthesis enzyme genes, such as *PSPH* and and *DTYMK*. Forced PSPH and DTYMK over-expression partially reverses the effects. In mice xenografted with hepatocellular carcinoma cells, treatment with B029-2 significantly reduces tumor progression, which correlates with hepatocellular carcinoma cell growth inhibition *in vivo* (Cai et al. 2021) (Table 1).

DS-9300, another p300/CBP HAT inhibitor, reduces prostate cancer cell proliferation and survival with an IC_{50} value of low nanomolar concentrations, and blocks prostate cancer progression in mouse models in a dose-dependent manner without a significant effect on body weight (Kanada et al. 2023) (Table 1).

p300/CBP bromodomain inhibitors as novel anticancer agents

Treatment with the p300/CBP bromodomain inhibitor CPI644, CBP30 or GNE-049 reduces histone H3K27 acetylation at enhancer- and super-enhancer-associated androgen receptor target genes such as *CCND1*, reduces gene transcription, and thereby induces prostate cancer and breast cancer cell growth inhibition (Garcia-Carpizo et al. 2019; Waddell et al. 2021). In lung squamous cell carcinoma, the majority of tumor tissues harbor *SOX2* gene gain, and SOX2 promotes tumorigenesis by interacting with p300 and thereby regulating target gene expression. Treatment with CBP30 suppresses SOX2 target gene expression, reduces lung squamous cell carcinoma cell proliferation, and substantially augment the anticancer effects of the PI3K inhibitor BKM120 (Kim et al. 2017) (Table 2).

The p300/CBP bromodomain inhibitors GNE-781 also show anticancer effects. GNE-781 reduces *FOXP3* expression in acute myeloid leukemia cells and suppresses leukemia progression in a mouse model (Romero et al. 2017). In NUT midline carcinoma cells, treatment with GNE-781 and a BET bromodomain inhibitor cooperatively down-regulates *MYC* transcription as well as NUT midline carcinoma cell proliferation (Morrison-Smith et al. 2020) (Table 2).

Treatment of acute myeloid leukemia cells with the p300/CBP bromodomain inhibitor I-CBP112 causes cell differentiation, suppresses clonogenic capacity, and reduces leukemogenesis potential *in vitro* and in a murine model; and I-CBP112 in combination with BET bromodomain inhibitors or the chemotherapy agent doxorubicin synergistically induces leukemia cell death (Picaud et al. 2015). Interestingly, I-CBP112 synergizes with the p300/CBP HAT inhibitor A-485 to reduce the transcription of androgen receptor target genes including *MYC* and to block prostate cancer cell proliferation (Zucconi et al. 2019). In addition, I-CBP112 suppresses ATP-binding cassette transporter gene expression; causes daunorubicin, doxorubicin and methotrexate accumulation; and sensitizes lung, breast and liver cancer cells to the chemotherapy agents (Picaud et al. 2015; Strachowska et al. 2021) (Table 2).

The p300/CBP bromodomain inhibitors CCS1477 and Y08284 suppress prostate cancer cell multiplication in cell culture and prostate tumor growth in mouse models (Welti et al. 2021; Xiang et al. 2022). Mechanistically, CCS1477 decreases *MYC* and androgen receptor and the expression of their target genes *in vitro* and *in vivo* (Welti et al. 2021). In acute myeloid leukemia and multiple myeloma cells, CCS1477 downregulates MYB and FGFR3 target gene expression and induces cell differentiation, and combination therapy with CCS1477 and standard-of-care agents blocks cancer progression in multiple mouse models (Nicosia et al. 2023) (Table 2). In acute myeloid leukemia cells characterized by myelodysplastic syndrome, CBP is one of the key factors for cell resistance to the DNA methylation inhibitor azacytidine, and combination therapy with CCS1477 and A-485 synergistically reduces the expression of protein synthesis genes and display synergistic effects with azacytidine against acute myeloid leukemia due to myelodysplastic syndrome (Diesch et al. 2021). In NUT midline carcinoma cells, combination therapy with CCS1477 and a BET bromodomain inhibitor synergistically reduces *MYC* gene expression, induces

NUT midline carcinoma cell apoptosis in cell culture, and leads to tumor regression at clinically relevant doses in three mouse models of NUT midline carcinoma, demonstrating that the combination therapy can be translated into clinical trials in patients (Tontsch-Grunt et al. 2022).

Dual p300/CBP and BRD4 bromodomain inhibitors as novel anticancer agents

In a panel of 60 models from a variety of cancer types, the dual p300/CBP and BRD4 bromodomain inhibitor NEO2734 shows antiproliferative activity in the majority of human tumor cell lines, and the strongest effects have been discovered in prostate, ovarian and colorectal cancer, lymphoma and leukemia cells. NEO2734 suppresses oncogene transcription, induces lymphoma and acute myeloid leukemia cell death, and blocks lymphoma and acute myeloid leukemia progression in mouse models, more effective than single-target p300/CBP or BRD4 inhibitors or the other dual p300/CBP and BRD4 inhibitor NEO1132 (Spriano et al. 2020; van Gils et al. 2021). Importantly, NEO2734 reduces histone H3K27 acetylation, the transcription of androgen receptor targets including *RAC1* and *MYC*, prostate cancer cell division in cell culture and tumor growth in mouse models, more substantially than BRD4 inhibitor and p300/CBP bromodomain inhibitor combination therapy (He et al. 2021; Yan et al. 2019) (Table 3). Additionally, NEO2734 considerably suppresses BRD4 inhibitor-resistant and anti-androgen agent enzalutamide-insensitive prostate cancer cell organoid growth *in vitro* and tumor growth in mice. The data further demonstrate the superiority of the dual p300/CBP and BRD4 bromodomain inhibitor NEO2734 as an anticancer agent (He et al. 2021; Yan et al. 2019).

CN470, another dual CBP/p300 and BRD4 bromodomain inhibitor, decreases the transcription of oncogenes including *MYC* and causes cell cycle arrest at the G1 phase and apoptosis in acute lymphoblastic leukemia cells characterized by mixed-lineage leukemia gene rearrangement (Imayoshi et al. 2022). In mice xenografted with acute lymphoblastic leukemia cell lines or patient-derived xenograft leukemia cells, treatment with CN470 results in prolonged survival compared to the vehicle control group, further demonstrating the superiority of dual CBP/p300 and BRD4 bromodomain inhibitors (Imayoshi et al. 2022) (Table 3).

PROTAC p300/CBP protein degraders as novel anticancer agents

P300 expression in tumor tissues has been found to be an independent marker for poor clinical outcomes in neuroblastoma patients (Durbin et al. 2022). The PROTAC p300 protein degrader JQAD1 induces p300 protein ubiquitination and degradation, suppresses critical oncogene transcription, causes neuroblastoma cell death in cell culture, and represses tumor growth in murine models (Durbin et al. 2022) (Table 3).

The PROTAC p300/CBP protein degrader QC-182 effectively induces p300/CBP degradation, significantly reduces p300/CBP-mediated gene transcription, and more effectively causes hepatocellular carcinoma cell growth suppression compared to its parental p300/CBP bromodomain inhibitor CCS1477. Importantly, QC-182 reduces p300/CBP protein expression in tumor tissues and decreases tumor progression in murine models of hepatocellular carcinoma (Chang et al. 2024) (Table 3).

JET-209, another PROTAC degrader of p300/CBP proteins, reduces acute lymphoblastic leukemia cell proliferation, much more potently than p300/CBP HAT and bromodomain inhibitors. JET-209 also effectively suppresses leukemia progression in mouse models without toxicity to normal tissues (Thomas et al. 2023) (Table 3).

Promising early data from clinical trials of p300/CBP inhibitors

CCS1477, a p300/CBP bromodomain inhibitor known as inobrodib in early stage clinical trials, is under investigation in patients with advanced tumours, such as metastatic anti-androgen treatment-resistant prostate cancer and tumors with biomarkers suggesting treatment response such as p300/CBP gene mutations or ARID1A or androgen receptor gene rearrangements or amplifications (Crabb et al. 2021) as well as haematological malignancies, such as relapsed or refractory acute myeloid leukemia and multiple myeloma (ClinicalTrials.gov Identifier: NCT04068597) (Nicosia et al. 2023). In the clinical trials, CCS1477 reduces MYC and Ki-67 expression in tumor tissues from metastatic castration-resistant prostate cancer patients (Crabb et al. 2021), induces leukemia cell differentiation in acute

myeloid leukemia patients, and results in substantial falls in serum and urinary biomarkers for myeloma in myeloma patients who have failed multiple other treatments (Nicosia et al. 2023). In the clinical trial involving leukemia and myeloma patients, approximately one-third of patients showed a therapeutic response to CCS1477 monotherapy, with progression-free survival in some cases sustained for more than 12 months (Nicosia et al. 2023). The two clinical trials of CCS1477 in patients with advanced solid tumours (Crabb et al. 2021) or haematological malignancies (Nicosia et al. 2023) are ongoing, the early data are encouraging but safety profiles and any potential mechanisms of resistance have not been disclosed (Table 4).

Although unpublished, FT-7051, another powerful p300/CBP bromodomain inhibitor, shows anticancer activity in mouse models of androgen receptor inhibitor-resistant prostate cancer. Very early results from metastatic castration-resistant prostate cancer patients in an open-label Phase I clinical trial reveals that mild or moderate treatment-emergent adverse events including hyperglycemia occur in 80% patients treated with FT-7051 monotherapy, and that FT-7051 monotherapy leads to a predicted efficacious exposure threshold consistent with pharmacokinetic/efficacy modeling (ClinicalTrials.gov Identifier NCT04575766) (Armstrong et al. 2021) (Table 4).

The dual p300/CBP and BRD4 bromodomain inhibitor NEO2734, also known as EP31670, recently entered clinical trials in patients with targeted advanced tumors including metastatic or unresectable NUT midline carcinoma, relapse or refractory anti-androgen-resistant prostate cancer, or other types of relapsed or refractory solid tumors with pathological and/or biological features suggesting a potential benefit from dual p300/CBP and BRD4 inhibition (ClinicalTrials.gov Identifier: NCT05488548). Unfortunately, no results from the NEO2734 clinical trial have been reported (Table 4).

Comparison between p300/CBP inhibitors/protein degraders and HDAC inhibitors

While the p300/CBP inhibitors and protein degraders exert anticancer effects mainly through inducing H3K27 deacetylation at enhancers, super-enhancers and promoters and thereby reducing oncogene transcription, HDAC inhibitors induce anticancer effects through blocking the effects of HDACs at tumor suppressor gene promoters and thereby activating tumor suppressor gene transcription (Falkenberg and Johnstone 2014; Jones et al. 2016). It can thus be presumed that p300/CBP inhibitors/protein degraders and HDAC inhibitors can be used to treat cancer where oncogene overexpression or tumor suppressor silencing is the key tumorigenic driver, respectively.

Unlike p300/CBP inhibitors or protein degraders, HDAC inhibitors have been extensively tested in clinical trials involving patients with cancer in a variety of organs. Several HDAC inhibitors, such as panobinostat and vorinostat, have been approved by the US Food and Drug Administration for the treatment of solid tumors or hematological malignancies. However, it is now evident that HDAC inhibitors need to be combined with the right anticancer agents in order to produce significant anticancer effects in patients. (Falkenberg and Johnstone 2014; Jones et al. 2016). There have been no reports on HDAC inhibitor and p300/CBP inhibitor combination treatment.

Discussions

p300/CBP induce histone H3K27 acetylation at gene promoters, enhancers and super-enhancers, resulting in oncogenic gene transcription and expression, tumor initiation and progression across a variety of cancer types, including melanoma, hepatocellular carcinoma, glioblastoma, sarcoma, leukemia, lymphoma, lung, breast, prostate and renal cancer.

The discoveries of p300/CBP HAT, bromodomain, or dual p300/CBP and BRD4 bromodomain small molecule inhibitors, as well as PROTAC p300/CBP degraders result from lab-based compound library screens, in silico screens and medicinal chemistry. Notable among these inhibitors are the p300/CBP HAT inhibitors iP300w, CPI-1612, B029-2, B026, A-485 and DS-9300; the bromodomain inhibitors CCS1477, FT-6876, GNE-781, GNE-049 and CBP30; and dual p300/CBP and BRD4 bromodomain inhibitors NEO2734 and CN470; and PROTAC p300/CBP degraders JQAD1 and JET-209; all of which effectively suppress p300/CBP at concentrations below 50 nM. Dual p300/CBP and BRD4 bromodomain inhibitors are likely to have better clinical application in the future than p300/CBP HAT or bromodomain inhibitors for cancer therapy, as they also effectively suppress the function of BRD4, another

Table 4 Promising early data from clinical trials of p300/CBP inhibitors

Inhibitors	Clinical trial	Early data from the clinical trial	ClinicalTrials gov Identifier & References
CCS1477	Phase I/IIa clinical trial in patients with advanced tumors, such as anti-androgen treatment-resistant prostate cancer and tumors with biomarkers suggesting treatment response such as p300/CBP gene mutations or ARID1A or androgen receptor gene rearrangements or amplifications	CCS1477 reduces MYC and Ki-67 expression in tumor tissues from patients with metastatic castration-resistant prostate cancer. No further information is available	NCT03568656 (Crabb et al. 2021)
CCS1477	Phase I/IIa clinical trial in patients with haematological malignancies, such as relapsed or refractory acute myeloid leukemia and multiple myeloma	One-third of patients showed a therapeutic response to CCS1477, with progression-free survival in some cases sustained for more than 12 months. CCS1477 results in substantial falls in serum and urinary biomarkers for myeloma in myeloma patients who have failed multiple other treatments	NCT04068597 (Nicosia et al. 2023)
FT-7051	Open-label Phase I clinical trial in patients with metastatic castration-resistant prostate cancer resistant to androgen receptor inhibitors	A predicted efficacious exposure threshold consistent with pharmacokinetic/efficacy modeling. Mild or moderate treatment-emergent adverse events including hyperglycemia in 80% patients	NCT04575766 (Armstrong et al. 2021)
NEO2734	A phase I clinical trial in patients with relapse or refractory castration-resistant prostate cancer, metastatic or unresectable NUT midline carcinoma, or other types of relapsed or refractory solid tumors	No results are available	NCT05488548

key regulator of enhancer activity, oncogene transcription and tumorigenesis. Compared with p300/CBP HAT, bromodomain or dual p300/CBP and BRD4 bromodomain inhibitors, PROTAC degraders:

(i) Are likely to show a clear preference for p300 relative to CBP, or vice versa, thus providing better specificity in cancers due to one of the two proteins, such as neuroblastoma (Durbin et al. 2022), but less efficacy in cancers due to both p300/CBP;.
(ii) Are likely to exhibit limited toxicity if the PROTAC degraders target p300 or CBP, but not both;.
(iii) Often demonstrate higher potency than their parental inhibitors.

The p300/CBP inhibitors and degraders reduce histone H3K27 acetylation at oncogene loci, resulting in oncogene expression repression, cancer cell growth arrest and apoptosis, immune response suppression, and tumor growth inhibition. However, there have been no reports on systematic toxicology studies of p300/CBP inhibitors or protein degraders in mice, as the researchers did not examine blood, liver or kidney samples from mice treated with p300/CBP inhibitors or protein degraders. Strategies to mitigate toxicity and enhance the therapeutic index of these inhibitors include combination therapy with low doses of p300/CBP inhibitors and low doses of other anticancer agents. Importantly, p300/CBP inhibitors show synergistic/co-operative effects against a range of cancers when in combination with radiotherapy and chemotherapy agents such as temozolomide and doxorubicin, as well as targeted therapy agents such as DNA and histone methylation inhibitors and BRD4 inhibitors. Of particular significance, the p300/CBP bromodomain inhibitors CCS147 and FT-7051 and the dual p300/CBP and BRD4 bromodomain inhibitor NEO2734 have advanced to clinical trials in cancer patients with encouraging early results, highlighting their potential as therapeutic agents in cancer treatment.

PROTAC technology has recently emerged as a very promising strategy to effectively target oncogenic proteins for demolition. The small molecule PROTACs ARV-110 and ARV-471 target androgen receptor and oestrogen receptor for ubiquitination and degradation, and have entered clinical trials in prostate and breast cancer patients, respectively (Békés et al. 2022). As p300/CBP bromodomain inhibitors synergize with HAT inhibitors to reduce oncogene transcription, tumor cell multiplication *in vitro* and tumor growth in mouse models (Diesch et al. 2021; Zucconi et al. 2019), PROTAC p300/CBP protein degraders JQAD1, QC-182, and more effectively, JET-209 can induce the degradation of p300/CBP proteins by up to 95%, reduce oncogene transcription, blocks tumor cell multiplication in cell culture and tumor growth in murine models. It is anticipated that PROTAC p300/CBP degraders will be advanced into clinical trials in patients.

Future directions

Future efforts in drug development should prioritize the generation of more specific and efficacious inhibitors of p300/CBP HAT activity, dual p300/CBP and BRD4 bromodomain inhibitors, and PROTAC p300/CBP degraders. These endeavors can be pursued through a combination of virtual screen, artificial intelligence-guided virtual screen and wet laboratory screen of small molecule compounds, medicinal chemistry synthesis, and artificial intelligence-guided design of new compounds or modification of existing compounds for better selectivity or efficacy. It is imperative to evaluate the impact of these agents on normal cells to ensure their specificity against cancer cells. To assess the pharmacodynamics, pharmacokinetics, metabolism and anticancer efficacy of these compounds, comprehensive studies should be conducted using *in vitro* models and mouse models. It is equally important to perform systematic toxicology studies of these p300/CBP-targeting anticancer agents, such as blood, liver and kidney toxicity analyses, in preclinical mouse models.

There have been no reports on cancer cell resistance to p300/CBP inhibitors or PROTAC degraders. Future research needs to be conducted to establish *in vitro* and *in vivo* models of cancer cell resistance or insensitivity to p300/CBP inhibitors and PROTAC degraders, to investigate the mechanisms of cancer cell resistance or insensitivity, to explore alternative targets in the p300/CBP oncogenic pathway, and to develop novel therapies combining p300/CBP inhibitors/PROTAC degraders with more established anticancer agents to overcome cancer cell resistance or

insensitivity. Furthermore, identifying other anticancer agents that exhibit the most efficacious synergy when combined with p300/CBP inhibitors/PROTAC degraders is crucial, and this can be achieved through CRISPR-Cas9 gene knockout screen and approved drug library screen, followed by validation *in vitro* and in mouse models. Ultimately, the most efficacious combination therapies should undergo further preclinical testing to assess pharmacodynamics, pharmacokinetics, metabolism and anticancer efficacy for eventual clinical trials in cancer patients, leading to better survival, little toxicity to normal malignant cells, and better quality of life.

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