



Human Cyclin-Dependent Kinase 12 (CDK12), Kinase Domain



A Target Enabling Package (TEP)

Gene ID / UniProt ID / EC	CDK12, 51755 / Q9NYV4 / 2.7.11.22, 2.7.11.23 CCNK, 8812 / O75909 / -
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Target PI	Alex Bullock (SGC Oxford)
Therapeutic Area(s)	Oncology
Disease Relevance	CDK12 loss sensitises cancer cells to DNA damage
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SUMMARY OF PROJECT

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Cyclin-dependent kinase 12 (CDK12) phosphorylates RNA Pol II C-terminal domain (CTD) to promote transcriptional elongation of large DNA damage response genes. CDK12 is frequently mutated or amplified in cancer and its loss sensitises cells to DNA damage. Here we present 3 crystal structures of the human CDK12/CycK complex including apo, AMP-PNP and covalent inhibitor complexes. Kinase assays compare domain truncations and report the K_m values for substrate. THZ531 is presented as a potent and selective inhibitor of CDK12 with nanomolar activity in leukemic cell lines.

SCIENTIFIC BACKGROUND

Human CDK12 is an unusually large CDK family member (1,490 a.a.) that assembles with cyclin K (CCNK, or CycK). The CDK12/CycK complex phosphorylates Ser2 in the heptad repeats of the RNA Pol II CTD promoting transcriptional elongation of large DNA damage response genes, including BRCA1/2, ATR and FANCI. Loss of CDK12 function sensitizes ovarian cancer cells to cisplatin and PARP inhibitors. CDK12 inhibition may therefore form a general strategy for radiosensitization in oncology. CDK12 is co-amplified with HER2 (ERBB2) in ~20% of breast tumours; overexpression correlates with high proliferative index and grade 3 tumour status based on tissue microarrays. Conversely, some 13% of breast cancers and 5% of ovarian cancers harbour loss of function CDK12 mutations, while disruptive CDK12-HER2 gene fusions occur in breast and gastric cancers. Thus, CDK12 may have both pro-oncogenic and tumour suppressor function depending on context. No specific inhibitors have been described to date. We aimed to (i) establish protocols for recombinant expression; (ii) solve and characterise the structure and activity of the CDK12/CycK complex; and (iii) identify a potent and selective CDK12 inhibitor.

RESULTS – THE TEP

Proteins purified

CDK12⁷¹⁵⁻¹⁰³⁸/CycK¹¹⁻²⁶⁷ complex (used for crystallography, assays)

Human CDK12 (a.a. 715-1038) and CycK (a.a. 11-267) were each cloned into pFB-LIC-Bse, co-expressed in Sf9 cells and purified using Ni-affinity and size exclusion chromatography.

CDK12⁷¹⁵⁻¹⁰⁵²/CycK¹¹⁻²⁶⁷ complex (used for crystallography, assays)

Human CDK12 (a.a. 715-1052) and CycK (a.a. 11-267) were each cloned into pFB-LIC-Bse, co-expressed in Sf9 cells and purified using Ni-affinity and size exclusion chromatography.

Full length CDK12/CycK complex (used for in vitro kinase assays)

6xHis-CDK12/GST-CycK or GST-CDK12/6xHis-CycK were prepared by baculoviral co-expression and purified sequentially using Ni-affinity and glutathione sepharose chromatography (Invitrogen pDEST10 and pDEST20 vectors).

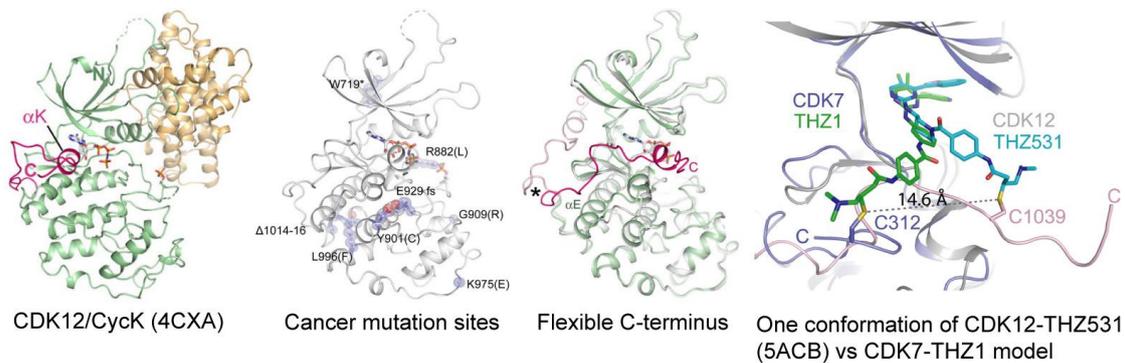
Note, soluble expression of CDK12 was only observed upon co-expression with CycK. Phosphorylated CDK12 was optimally obtained by additional co-expression of yeast CAK.

RNA Pol II CTD (used for in vitro kinase assays)

GST-CTD substrate containing all 52 heptad repeats was cloned into Creator System plasmid V1544 for bacterial expression and glutathione sepharose chromatography purification.

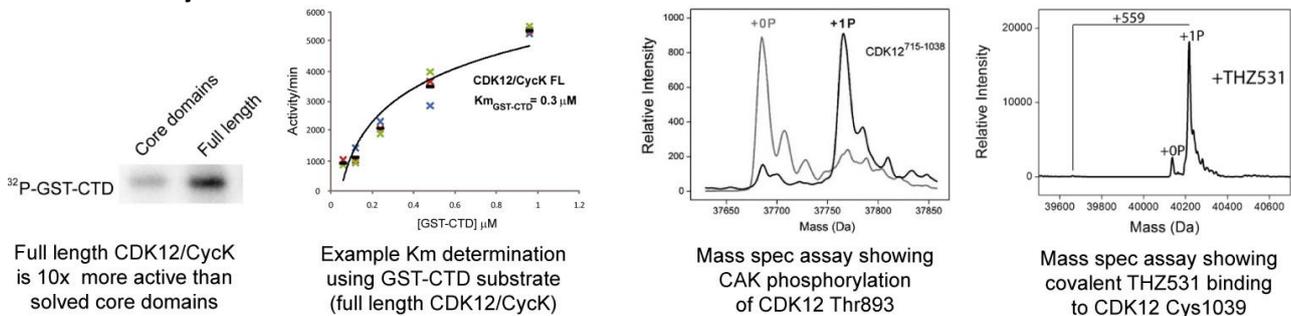
Structural data

1. Core structure of apo CDK12⁷¹⁵⁻¹⁰³⁸/CycK¹¹⁻²⁶⁷ complex (3.15 Å, PDB: [4UNO](#) supersedes [4CJY](#))
2. Extended structure of CDK12⁷¹⁵⁻¹⁰⁵²/CycK¹¹⁻²⁶⁷ complex with AMP-PNP (3.15 Å, PDB: [4CXA](#)).
3. THZ531 inhibitor bound structure of CDK12⁷¹⁵⁻¹⁰⁵²/CycK¹¹⁻²⁶⁷ complex (2.7 Å, PDB: [5ACB](#)).



The structures capture the phosphorylated (pT893) active kinase conformation. Two novel features for a CDK were identified (i) a large β 4- β 5 loop insertion that contributes to the specific N-lobe interaction with CycK; and (ii) a C-terminal kinase extension (α K helix) observed in alternative conformations that open and close the ATP pocket and allows for covalent inhibitor design. Binding interactions were defined for AMP-PNP and the covalent inhibitor THZ531, which binds irreversibly to Cys1039 in two conformations of the C-terminal kinase extension. Sequence alignment and modelling shows that CDK12 Cys1039 adopts a distinct position to CDK7 Cys312 (which binds THZ1, (1)) allowing for kinase selectivity.

***In vitro* assays**



In vitro kinase assay:

Activity assays were performed using 32 P-ATP and GST-CTD as substrates and measured by radiography. The full length (FL) CDK12/CycK complex was 10x more active than the core domains solved by crystallography. $K_{m\text{ATP}}$ values for the full-length and core complexes were 2 μ M and 25 μ M, respectively. $K_{m\text{GST-CTD}}$ values for the full-length and core complexes were 0.3 μ M and 2 μ M, respectively. Kinases were present at 13 nM concentration.

CAK assay:

Intact mass spec showed that yeast CDK-activating kinase (CAK) could phosphorylate the CDK12 activation loop residue Thr893.

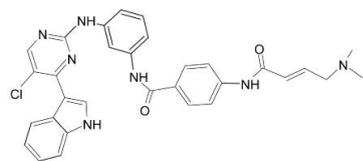
Covalent inhibitor binding assay:

THZ series derivatives were screened for covalent CDK12 binding by mass spec. Domain mapping experiments confirmed Cys1039 as the covalent attachment site. CDK12⁷¹⁵⁻¹⁰⁵² could be fully labelled with THZ531, whereas CDK12⁷¹⁵⁻¹⁰³⁸ was resistant.

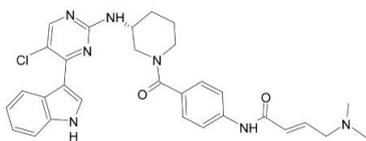
Chemical starting points

Chemical matter with co-structures included AMP-PNP as well as the novel covalent inhibitor THZ531 developed by Nathanael Gray with the following characterisation: (i) KiNativ profiling against 213 targets showed CDK12 and CDK13 as the only proteins labelled >55%; (ii) time dependent IC_{50} values (30 mins: CDK12, 158 nM; CDK13, 69 nM) with efficient labelling at 50 nM and 50-100 fold selectivity against CDK7 and CDK9; (iii) In cells, 50 nM THZ531 reduced expression of DNA damage response genes (e.g. BRCA1,

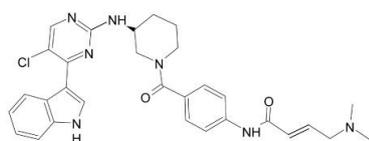
FANCF, ERCC4), while 200 nM reduced super-enhancer-associated transcription factors (e.g. RUNX1, MYB, TAL1, and GATA3); (iv) anti-proliferativity activity and apoptosis were observed in CML HAP1 cell line and Jurkat T-ALL cells (e.g. IC₅₀ = 50 nM, CellTiterGlo assay).



THZ1 (CDK7 selective)



THZ531 (CDK12/13 selective) Ligand Efficiency = 0.23
Ligand Lipophilicity Efficiency = 1.23



THZ532 (control isomer 50-100 fold weaker against CDK12/13)

IMPORTANT: Please note that the existence of small molecules within this TEP indicates that chemical matter can bind to the protein in a functionally relevant pocket. As such these molecules should not be used as tools for functional studies of the protein unless otherwise stated as they are not sufficiently potent or well-characterised to be used in cellular studies. The small molecule ligands are intended to be used as the basis for future chemistry optimisation to increase potency and selectivity and yield a chemical probe or lead series.

New literature since TEP approval

The group of Matthias Geyer have published the crystal structure of the CDK13/CycK complex (PDB [5EFQ](#), Cell Rep (2016) 14, 320-31). Chemical screening using the CDK12 inhibitor THZ531 has revealed that Ewing sarcoma cells are especially sensitive to CDK12 inhibition (Cancer Cell (2018), 33, 202-216). A synthetic lethality of CDK12 inhibition with the EWS/FLI is suggested based on tumour cell sensitivity to DNA damage. More recently, CDK12 has been shown to be targeted by molecular glue compounds that enable its binding to a DDB1-Cul4-Rbx1 complex where CDK12 acts as the E3 substrate recognition subunit to promote the ubiquitination and degradation of bound cyclin K resulting in loss of CDK12 activity (Nature (2020), 585, 293-297; Nat Chem Biol (2020), online Aug3; Elife (2020) 9:e59994).

Antibodies

CDK12 polyclonal antibodies (anti-rabbit) have been used by our collaborators and were kind gifts of Arno Greenleaf (original description in J Biol Chem 290, 1786-1795) or Jonathon Pines (original description in J Cell Sci 114, 2591-603).

CRISPR/Cas9 Reagents

CRISPR/Cas9 reagents targeting human CDK12 have been published by others in either CDK12-focussed research e.g. Cell Reports (2016) 17, 2367-2381, or in genomic studies e.g. Nat Biotech (2016) 34, 184-191. Latter reagents are available from Addgene (e.g. plasmids #75915, #75916, #75917). Alternatively, shRNA and siRNA reagents are commercially available from companies such as Dharmacon.

Future questions

- Further optimisation of chemical matter
- Further exploration of CDK12 as a therapeutic target in cancer cells

Collaborations

For more information regarding any aspect of TEPs and the TEP programme, please contact teps@thesgc.org

- Chemistry partner: Nathanael Gray, Harvard University
- Kinase Km assays: Gregg Morin, University of British Columbia

CONCLUSION

CDK12 maintains genomic stability and is a promising therapeutic target to sensitise cancer cells to DNA damaging agents. This TEP enabled the development of the first selective CDK12/13 inhibitor, THZ531, which shows evidence of anti-cancer activity through downregulation of both DNA damage response genes and super-enhancer associated transcription factors. Covalent targeting of cysteines remote from the ATP pocket represents a new mechanism for kinase inhibitor design.

THZ531 was developed by optimisation of the acrylamide linker in the CDK7 inhibitor THZ1. These inhibitors show overlapping activities. THZ1 has already demonstrated potent anti-cancer activity in leukaemic cells (2), MYCN-driven neuroblastoma cells (1), small cell lung cancer (3), triple-negative breast cancer (4), and oesophageal squamous cell carcinoma (5). It will be interesting in future to compare the therapeutic index of THZ531.

TEP IMPACT

Publications arising from this work:

- Dixon-Clarke SE, Elkins JM, Cheng SW, Morin GB, Bullock AN. (2015). [Structures of the CDK12/CycK complex with AMP-PNP reveal a flexible C-terminal kinase extension important for ATP binding](#). *Sci Rep.* 5, 17122.
- Zhang T, Kwiatkowski N, Olson, CM, Dixon-Clarke, SE, Abraham BJ, Greifenberg AK, Ficarro SB, Elkins JM, Liang Y, Hannett NM, Manz T, Hao M, Bartkowiak B, Marto JA, Geyer M, Bullock AN, Young RA, Gray NS. (2016) [Covalent targeting of remote cysteine residues to develop CDK12 and CDK13 inhibitors](#). *Nat Chem Biol.* 12, 876-84.

Futher impact

Work from this TEP has subsequently been developed in the wider literature. The compound THZ531 revealed that Ewing Sarcoma cells expressing the EWS/FLI gene fusion were exquisitely sensitive to CDK12 inhibition(6). Combined inhibition of CDK7, CDK12, and CDK13 also markedly downregulated MYC expression in ovarian cancer models to block tumour xenograft growth (7). Another study showed that cancer cells may develop resistance to THZ1 and THZ531 through the action of ABC-family drug transporters (8). However, these effects were circumvented using a resistant analogue, compound E9, that it exerted its cytotoxic effects through CDK12 (8). Further mechanistic insights into the role of CDK12 have been published by Dubbury et al. They identified that CDK12 acts to suppress intronic polyadenylation which is more prevalent in genes involved in homologous recombination (HR)-mediated DNA repair (9). Finally, further reagents and structures have been released. Scientists at Takeda have reported a novel CDK12 inhibitor series (10), while the Geyer lab have published the first structure of the CDK13/CycK complex (11).

FUNDING INFORMATION

The work performed at the SGC has been funded by a grant from the Wellcome [106169/ZZ14/Z].

ADDITIONAL INFORMATION

Structure Files

PDB ID	Structure Details
4UNO (supersedes 4CJY)	apo CDK12 ⁷¹⁵⁻¹⁰³⁸ /CycK ¹¹⁻²⁶⁷
4CXA	AMP-PNP bound CDK12 ⁷¹⁵⁻¹⁰⁵² /CycK ¹¹⁻²⁶⁷
5ACB	THZ531 bound CDK12 ⁷¹⁵⁻¹⁰⁵² /CycK ¹¹⁻²⁶⁷

Materials and Methods

Kinase Assay

Purified CDK complexes at 13 nM concentration were incubated in kinase assay buffer (50 mM Tris pH 7.5, 100 mM NaCl, 10 mM MgCl₂, 0.1% v/v NP-40, 1 mM DTT, 20 μM β-glycerophosphate, EDTA-free complete protease inhibitor cocktail) with varying amounts of cold ATP/ [γ-³²P]ATP and GST-CTD substrate which contains all 52 heptad repeats of human RNA Pol II C-terminal domain. Reactions were incubated in a circulating 30°C water bath for 15, 30 or 60 minutes. Kinase reactions were stopped with the addition of 6x SDS-PAGE loading dye. Samples were heated at 85°C for 5 minutes and resolved by 4-12% SDS-PAGE. Gels were subsequently dried on 3MM Whatmann paper and imaged with a FujiFilm FLA-7000 scanner. Phosphorylated bands were quantified using FujiFilm MultiGauge™ software. Kinetic parameters (Km values for ATP and GST-CTD) were determined from 2-3 independent experiments. Velocity and Lineweaver-Burke plots were analysed.

Mass spectrometry

Protein masses were determined using an Agilent LC/MSD TOF system with reversed-phase high-performance liquid chromatography coupled to electrospray ionization and an orthogonal time-of-flight mass analyser. Proteins were desalted prior to mass spectrometry by rapid elution off a C3 column with a gradient of 5-95% isopropanol in water with 0.1% formic acid. Spectra were analysed using the MassHunter software (Agilent).

Preparation of full length CDK12/CycK

Full length CDK12 Isoform 1 (NM_016507.2) and CycK1 were cloned into pDONR221 and recombined into bacmids using the Invitrogen Baculovirus Expression System with Gateway Technology. The full length proteins were N-terminally tagged with GST or 6xHis epitopes prior to bacmid generation as per manufacturer's conditions (Invitrogen pDEST10 and pDEST20 vectors). For expression of the full length CDK12/CycK1 complex, baculoviruses for the epitope-tagged CDK12 and CycK1 were co-infected at a ratio of 4:1 and incubated at 28°C with shaking at 150 rpm. Cells were harvested 48-72 hours post infection. The full length protein complexes were purified by tandem affinity chromatography using either combinations of 6xHis-CDK12/GST-CycK1 or GST-CDK12/6xHis-CycK1. Cell pellets were resuspended in CDK lysis buffer (10 mM Tris-HCl pH 7.5, 10 mM NaCl, 2 mM β-mercaptoethanol, 0.5 mM EDTA, 10 mM β-glycerolphosphate, 0.5 mM sodium orthovanadate, 2 mM NaF, 0.2% v/v NP-40 and EDTA-free complete protease inhibitor cocktail (Roche)). The lysate was incubated on ice for 30 minutes with an additional 0.5 M NaCl and occasional manual mixing. Lysate was then subjected to sonication and clarified by centrifugation. Proteins were captured overnight at 4°C using Ni-NTA agarose (Qiagen) that was pre-equilibrated with CDK equilibrium buffer (10 mM Tris-HCl pH 7.6, 500 mM NaCl, 10% glycerol, EDTA-free complete protease inhibitor cocktail). The Ni-NTA agarose was washed 3x with CDK equilibration buffer and the bead slurry transferred to a disposable column for step-wise elution using CDK equilibration buffer supplemented with 15, 25, 100 and 200 mM imidazole. The eluted protein complexes were dialyzed overnight against CDK activation buffer (12.5 mM Tris-HCl pH 7.5, 150 mM NaCl, 10 mM MgCl₂, 1 mM EGTA, 5 mM β-glycerolphosphate, 0.5 mM sodium orthovanadate, 2 mM DTT, 0.01% Triton X-100, 10% glycerol, EDTA-free complete protease inhibitor cocktail) to facilitate buffer exchange and removal of imidazole. The protein was concentrated using an Amicon filtration device with a 30 KDa molecular weight cut-off and the retentate was incubated with 500 μM ATP at 30°C for 1 hour to allow auto-activation of the CDK12 kinase. Subsequently, the proteins were further purified using glutathione

agarose beads (Pierce). Following overnight batch binding at 4°C, the beads were washed 4x with CDK activation buffer and the bead slurry transferred to a disposable column. Bound protein was eluted in a step-wise fashion with elution buffers (100 mM Tris-HCl pH 7.5, 300 mM NaCl, 1.0 mM EDTA, 0.04% Triton X-100, 4 mM DTT) supplemented with 10 mM and 20 mM glutathione. The purity of the eluted fractions was confirmed by SDS-PAGE or Western blotting before storage at -80°C in 50 mM Tris pH 7.5, 150 mM NaCl, 0.5 mM EDTA, 0.02% Triton X-100, 2 mM DTT, 50% glycerol. Protein concentration was determined by Bradford assay.

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