AI-driven Discovery and Profiling of GTAEXS-617, a Selective and Highly Potent Inhibitor of CDK7

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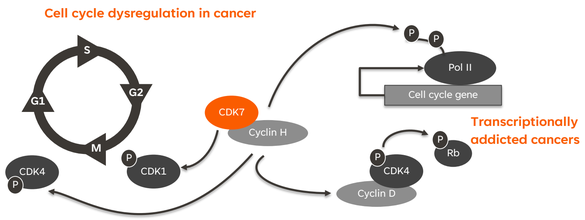
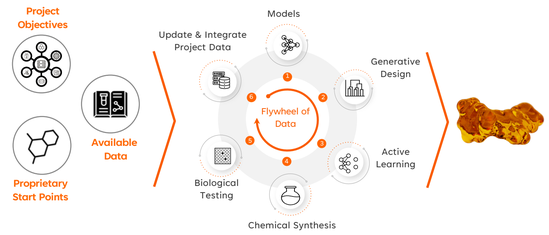
INTRODUCTION



Cyclin-dependent kinase 7 (CDK7) is an attractive therapeutic target in oncology, due to its dual role in regulating cell cycle progression and transcription, both dysregulated during tumourigenesis. Inhibiting CDK7 has been shown to severely limit the proliferative capacity of cancer cells *in vitro* and *in vivo*; however, developing effective CDK7 inhibitors (CDK7i) has proven challenging due to selectivity and tolerability issues, including GI tract toxicity.

METHODS



- Our AI platform and knowledge transfer from large kinase datasets were leveraged to identify starting points.
- Key objectives were to improve tolerability and reduce the side effects of CDK7i.
- *In vivo* PK data and *in vitro* endpoints from Caco-2 permeability were incorporated into multi-parameter optimisation to exploit active learning methods.
- Active learning algorithms provided an efficient search of chemical space to drive design towards potent and permeable compounds.
- Ranking of compounds to move into efficacy assays was performed via an automated pipeline for early human dose prediction.

RESULTS

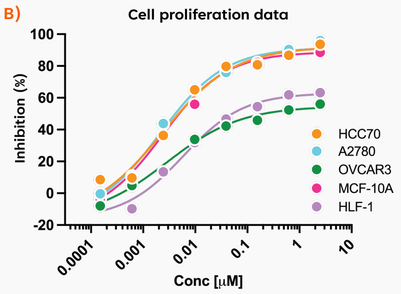
Figure 1: Rapid discovery of GTAEXS-617, a potent and permeable CDK7i

A)

Assay	Value
CDK7 pKD (SPR)	9.48
Caco-2 Papp (A-B)	5.3 10^{-6} cm/s
Caco-2 efflux ratio	4
Human microsome Clint	<3 µL/min/mg
Human hepatocyte Clint	2 µL/min/10^6 cell
Bioavailability mouse	77% from PK at 3 mpk

- From hit to candidate within 136 compounds
- Highly potent across cell lines
- Excellent drug like properties

B)



	Emax (%)	IC50 (µM)
HCC70	92.178	0.002
A2780	91.526	0.002
OVCAR3	54.783	0.003
MCF-10A	88.851	0.002
HLF-1	63.016	0.006

Figure 1: (A) Key GTAEXS-617 potency and ADMET profile features. (B) Anti-proliferative effects of GTAEXS-617 on ovarian, TNBC and normal cell lines.

Figure 2: Highly selective across whole kinome

A)

Kinase	pIC50	Fold Selectivity
CDK7	9.48*	–
CDK1	5.69	6166
CDK2	7.06	263
CDK9	5.48	10000
CDK12	6.13	2235
CDK13	6.37	1288
CDK16	6.50	794
CDK17	6.65	676
CDK18	6.99	309

C)

Kinase	% Inhibition at 3 µM
CDK7	97.8
CDK17	49.4
CDK16	46.8
MAP2K6	34.4
EIF2AK3	33.5
SLK	33.3

B)

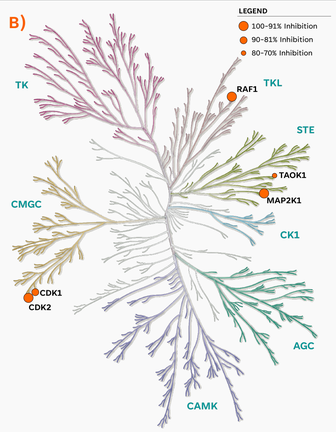


Figure 2: GTAEXS-617 fold selectivity against (A) other CDK family members (Km ATP), *pKD measured by SPR, (B) off-target activity against whole kinome run at 3 µM in kinase profiler assay at Eurofins. (C) Cell based kinase selectivity was assessed in ActivX KiNativ platform at 3 µM.

Figure 3: Tumour regression activity and tolerability observed in xenograft models

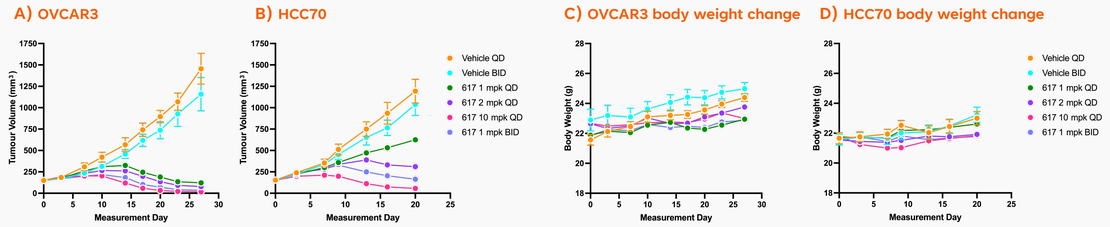


Figure 3: Efficacy of GTAEXS-617 at low doses in both ovarian and TNBC xenograft models (A) OVCAR3 and (B) HCC70. (C-D) GTAEXS-617 is well tolerated at efficacious doses in both models with no effect on body weight change.

Figure 4: AI platform leveraged to test ovarian cancer samples, revealing insight into heterogeneity in patient response

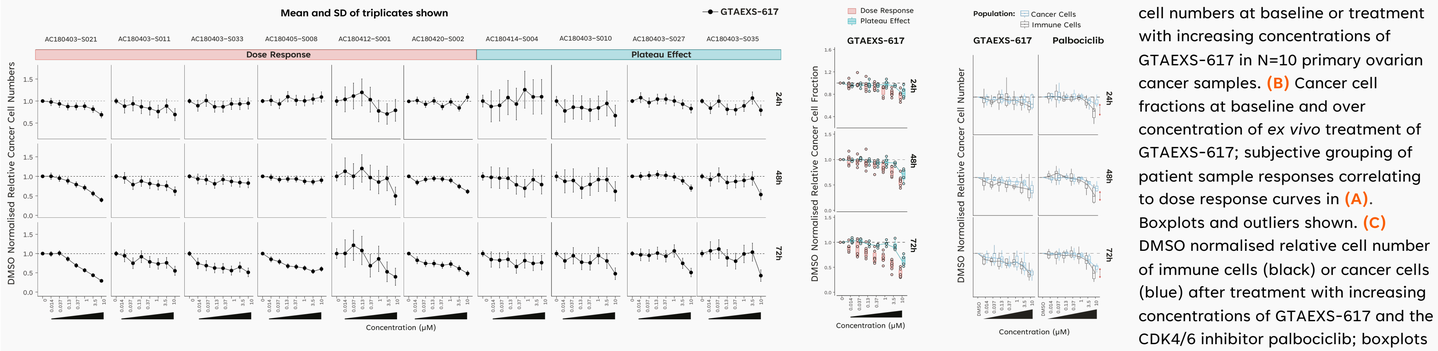


Figure 4: (A) DMSO normalised cancer cell numbers at baseline or treatment with increasing concentrations of GTAEXS-617 in N=10 primary ovarian cancer samples. (B) Cancer cell fractions at baseline and over concentration of *ex vivo* treatment of GTAEXS-617; subjective grouping of patient sample responses correlating to dose response curves in (A). Boxplots and outliers shown. (C) DMSO normalised relative cell number of immune cells (black) or cancer cells (blue) after treatment with increasing concentrations of GTAEXS-617 and the CDK4/6 inhibitor palbociclib; boxplots of N=10.

CONCLUSIONS

- Our AI-driven platform enabled rapid and efficient discovery of an orally bioavailable, selective small-molecule antagonist of CDK7 with high on-target potency: GTAEXS-617.
- Design criteria were met after synthesising only 136 compounds.
- Limitations traditionally associated with CDK7i were overcome during the design process, including efflux and unfavourable GI tract toxicity.
- Potent anti-tumour activity of GTAEXS-617 was shown *in vivo*.
- In primary ovarian cancer samples, two response groups appear to be forming following CDK7 inhibition, distinguished by dose response curves starting early versus a plateau effect.
- GTAEXS-617 tended to demonstrate less immune cell toxicity compared to a clinical CDK4/6 inhibitor.
- Researchers aim to leverage these insights to elucidate a patient selection or PD biomarker.
- These data support the advancement of our AI-designed CDK7i GTAEXS-617 towards clinical development.

AI-driven discovery of our CDK7i was rapid, efficient and provided early insights into patient response.

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