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Identification of an orally bioavailable dual Cyclin K glue degrader - CDK12/13 inhibitor

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I have the following financial relationships to disclose:

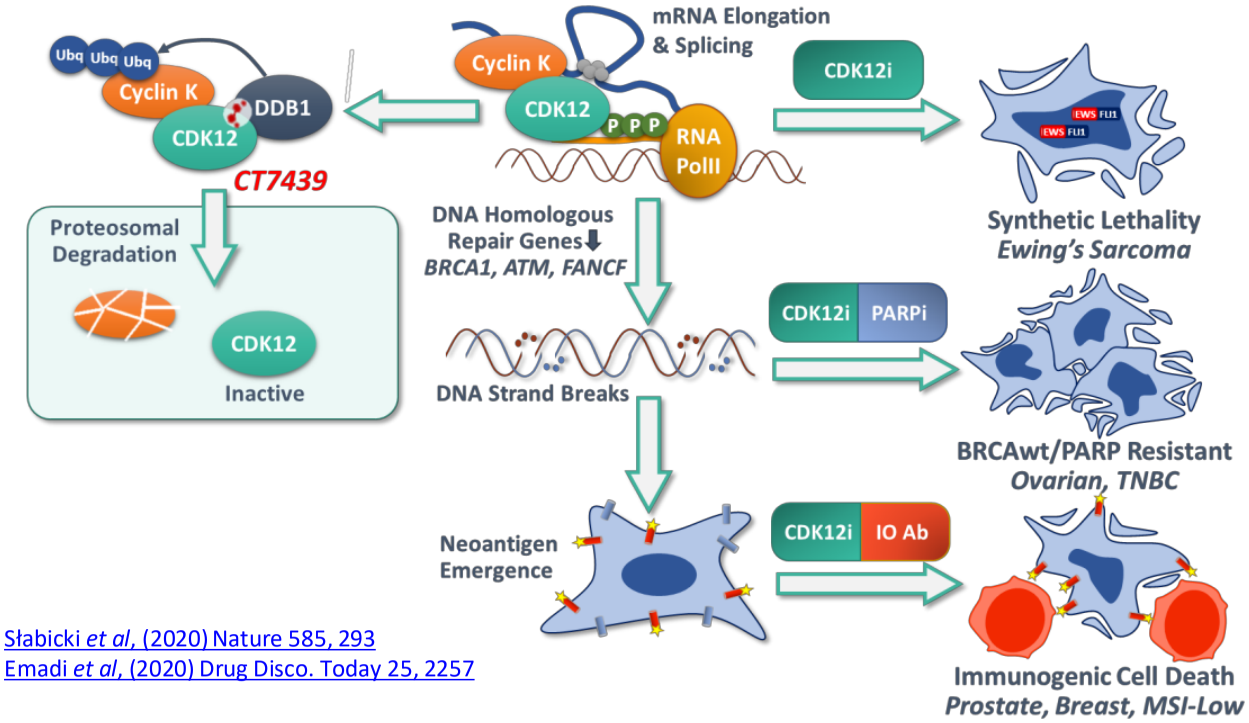
Stockholder in: Carrick Therapeutics Ltd., AstraZeneca PLC

Employee of: Carrick Therapeutics

I will not discuss off label use and/or investigational use in my presentation.

CDK12/13 inhibition through cyclin K degradation has broad potential as a therapeutic mechanism

- CDK12/13 are transcriptional regulators of DNA-repair genes: **Inhibition of CDK12/13 induces BRCAness in cells**
- Potential clinical opportunities:
  - Synthetic lethality in Ewing's Sarcoma (Iniguez AB, *et al*, Cancer Cell 2018; 33(2): 202-216)
  - Combination with PARP inhibition in BRCAwt or acquired resistance (Johnson et al, Cell Rep 2016; 17(9):2367-2381)
  - Combination with immune therapies, to enhance immune response (Li Y, *et al*, Cancer Lett. 2020; 495: 12-21)
  - CDK12/HER2 co-amplified tumours (inc. ADC combinations) (Choi HJ, *et al*, EMBO Rep. 2019; 20: e46058)

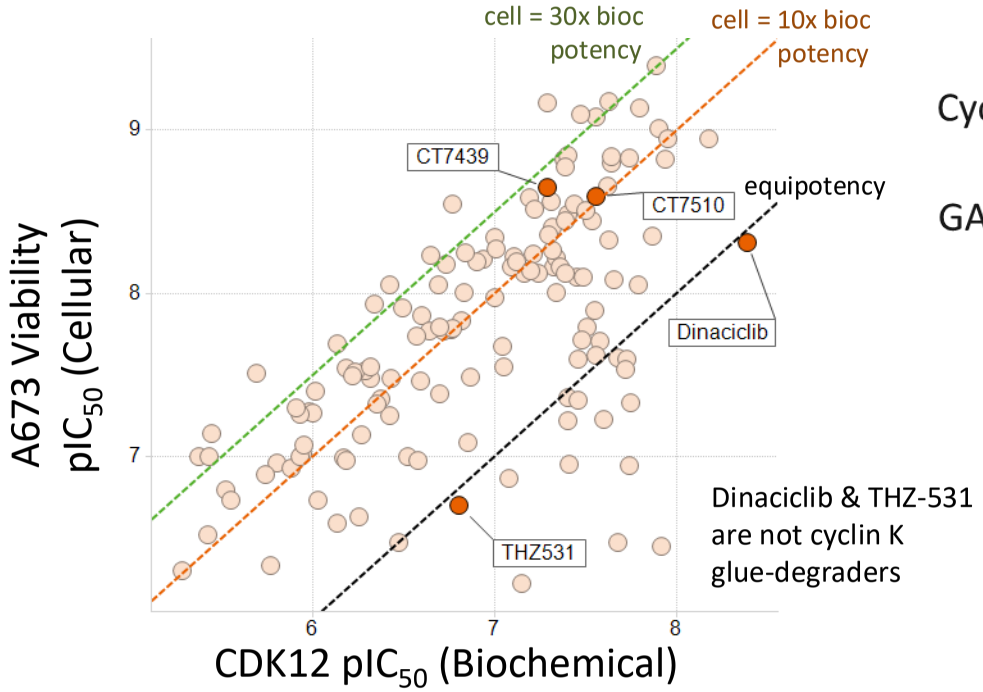


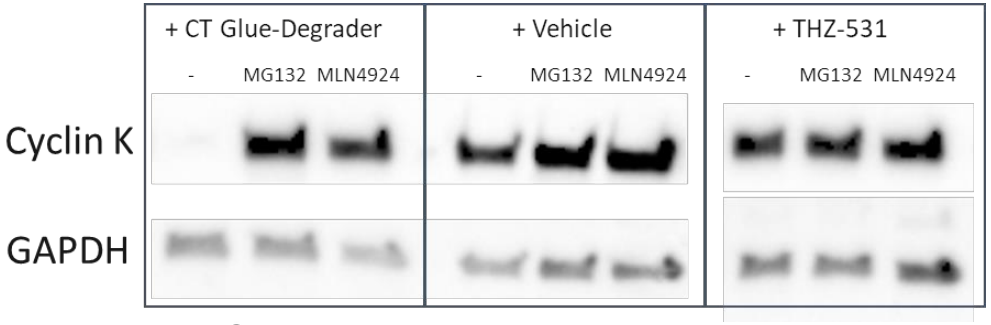
Słabicki *et al*, (2020) Nature 585, 293
Emadi *et al*, (2020) Drug Disco. Today 25, 2257

We have developed CDK12/13 inhibitors that display nM cellular potency achieved through dual mechanism of Cyclin K degradation and kinase inhibition

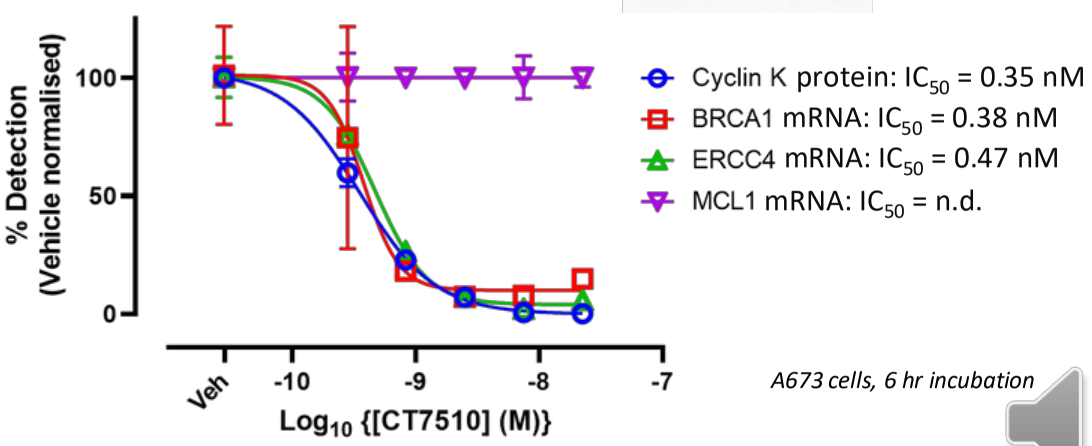
Optimisation of cellular potency identifies glue-degraders of Cyclin K

- Lead series of molecules with CDK12/13 inhibitory activity (Ainscow et al, AACR annual meeting 2020, Abs 5692)
- Many compounds show greater potency in cells vs. biochemical assays
- Optimisation in cellular assay identified glue-degrader molecules with potent transcriptional regulation





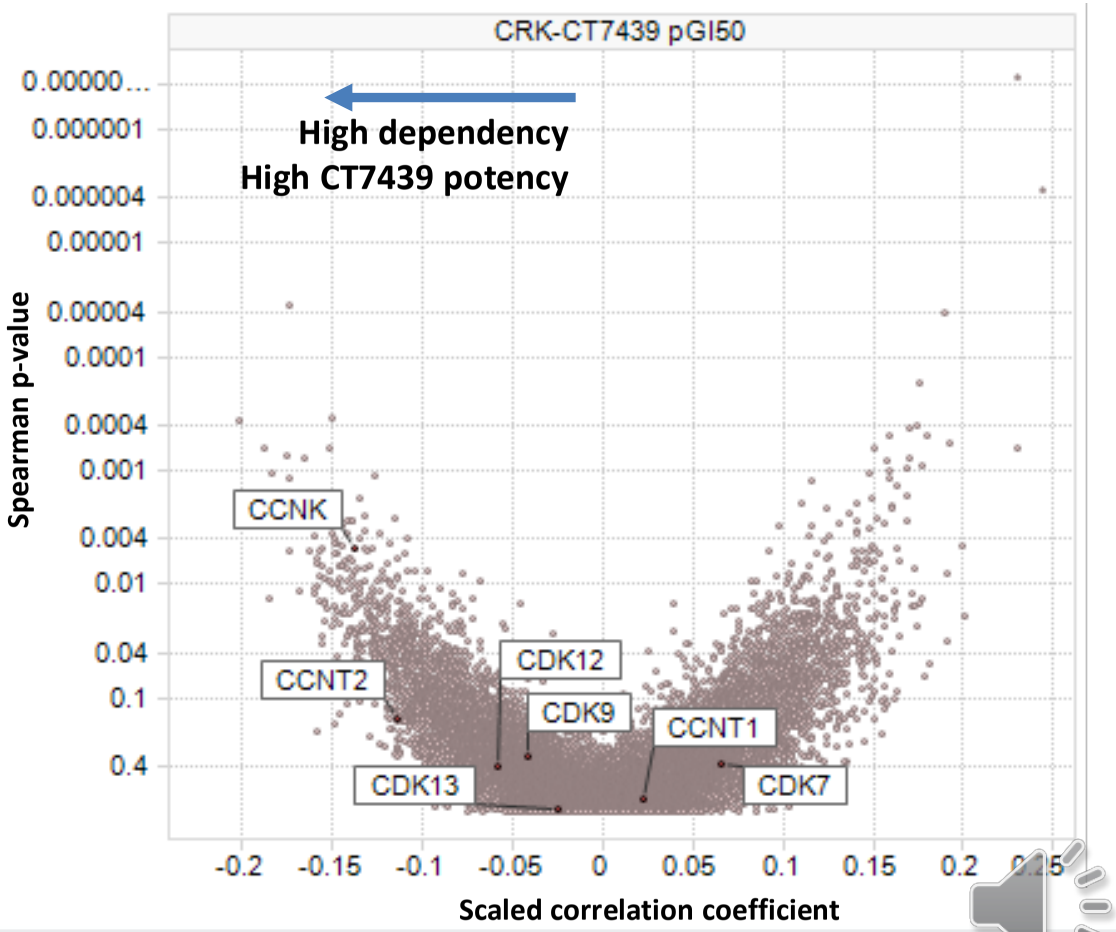
A673 cells, 2 hr incubation with 1 µM CDK12 inhibitor; 10 µM MG132 (proteosome inhibitor); 10 µM MLN4924 (neddylation inhibitor)



A673 cells, 6 hr incubation

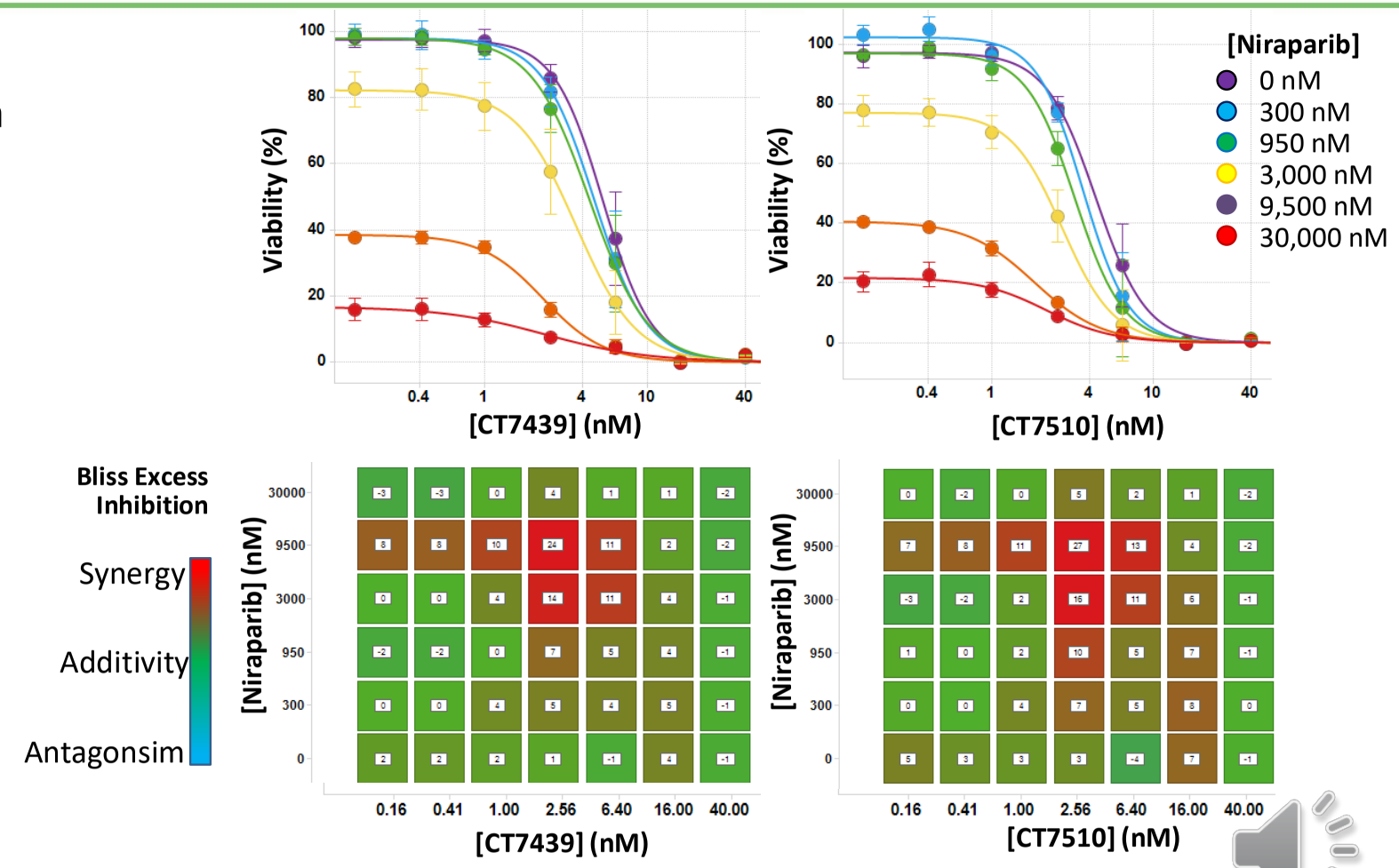
CT7439 mimics CCNK knockout

- Correlation of cell line sensitivity (n=69) to whole exome genetic dependency from CRISPR deletion screens (Depmap – 21Q2 dataset)
- Cyclin K knockout is highest ranked of all CDKs and cyclins
- Consistent with primary mechanism of action of CT7439 being through cyclin K degradation



CT7439 & CT7510 synergise with PARP inhibition

- CDK12 knockdown has been shown to lead to synthetic lethality with PARP inhibitors in BRCAwt ovarian cell lines (Joshi PM, *et al*, JBC 2014; 289: 9247-9253)
- Synergy demonstrated between CT7439 and CT7510 with PARP inhibition in the BRCAwt ovarian cell line, OV-90



Profile of candidate molecules

CT7439 & CT7510 are optimised CDK12/13 inhibitors/cyclin K glue-degraders

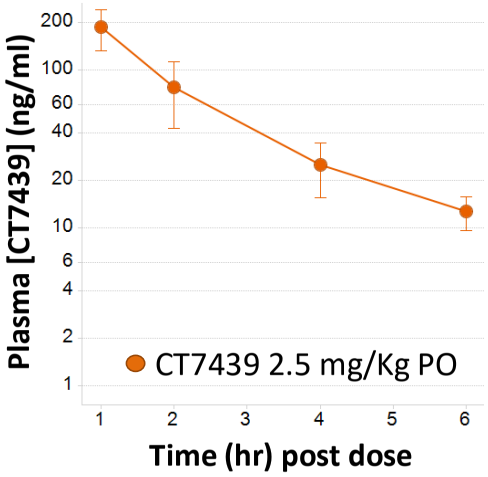
- Glue–degraders: Cellular potency reduced by proteosome inhibition
- No inhibition outside CDK family (Kinativ)
- Clean CYP and hERG profile (>1000x over cellular potency)
- Orally bioavailable – predicted once daily dosing

Molecule ID	CT7439	CT7510
CDK12/7 IC_{50} (nM)	**50**/320	**25**/250
A673 IC_{50} (nM)	**2.5**	**1.9**
A673 Δ IC_{50} +MLN4924	8x	5x
hERG IC_{50} (µM)	5.3	3.4
CYP IC_{50} (µM): 1A2 2C9 2C19 2D6 3A4/5	>20 12.1 >20 4.1 7.8	>20 12.6 > 20 >20 5.0
Microsome turnover: Mouse/Rat/Human (µl/min/mg)	7/25/39	12/20/30
Hepacyte turnover Mouse/Rat/Human (µl/min/10^6 cells)	41/30/26	26/11/12
PO AUC0-t (uM.hr) mouse (5 mg/Kg)	5.2	36.4

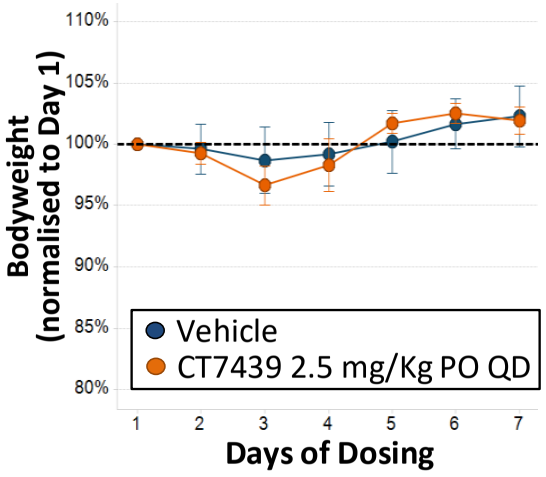
CT7439 is a potential first-in-class oral cyclin K degrader

- Nude mice bearing A673 (Ewing's sarcoma) tumours
- CT7439 dosed at 2.5 mg/Kg QD PO for 7 days then tumours analysed for Cyclin K
  - Good oral exposure
  - Well tolerated (no findings at necropsy)
  - Significant reduction in tumour cyclin K sustained for 24hr

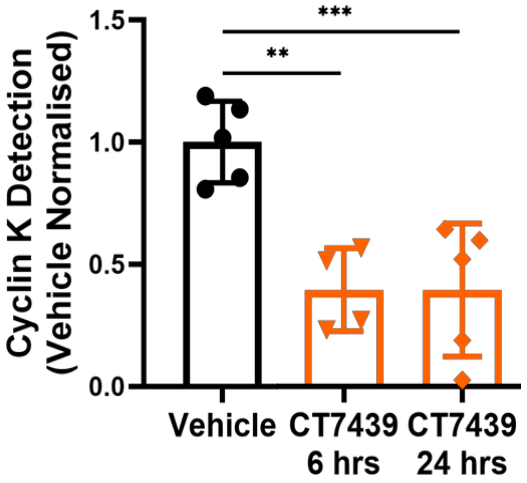
Pharmacokinetics



Bodyweight



Cyclin K protein in tumours



- **Identified potent glue-degraders of cyclin K**
- **CT7439 induces BRCAness to synergise with PARP inhibition**
- **CT7439 is well tolerated with oral bioavailability**
- **CT7439 is now being progressed in IND-enabling toxicity studies**

Acknowledgements

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