Defining Activity and Patient Selection of a Novel CDK7 Inhibitor, GTAEXS-617, Through AI-supported Primary Cancer Tissue Profiling

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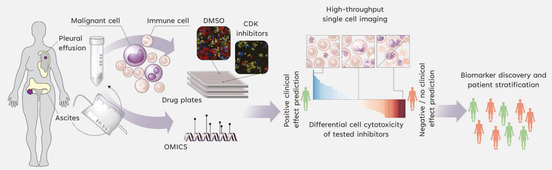
INTRODUCTION

Dual inhibition of CDK4/6 has become a mainstay treatment for several cancers, including HR-positive/ HER2-negative breast cancer. CDK7 represents another potentially attractive CDK target that could combine the cell cycle inhibition found in CDK4/6 inhibitors with inhibition of transcription. We have generated a highly potent, selective and bioavailable inhibitor of CDK7, GTAEXS-617 ('617).

CDK7 is expressed in both normal and diseased tissue, therefore understanding the expression, sensitivity profiles and effects of its inhibition in cancer and non-transformed cells (e.g. stromal or immune) is crucial to elucidate MOA and determine the therapeutic window. To identify those patients more likely to benefit from CDK7 inhibition and '617 therapy in particular, we have used machine learning and other approaches in part to analyse the multiparameter response in heterogeneous patient tissue samples.

METHODS



To fully understand the potency and activity of '617, including versus other CDK7 and CDK4/6 inhibitors, we deployed disease relevant primary sample model systems from, for instance, patients diagnosed with ovarian, breast or lung cancer or MCL that represent the cancer microenvironment.

Single cell *ex vivo* functional screening combined with transcriptomics after CDK7 perturbation in disease relevant primary human cancer samples helps reveal cancer-specific effects and patient selection methods. Our proprietary, translatable high-content imaging platform amenable to primary human material supported by deep learning-driven image analysis is used for all functional profiling.

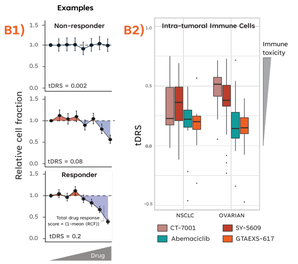
RESULTS

Figure 1: Primary cancer models across multiple indications reveal disease-subtype and patient-level sensitivities

A) Patient cohort

CHARACTERISTICS		COUNT (%)
OVERALL		53 (100%)
OVARIAN		30 (56.6%)
HGSOC	Newly diagnosed	10 (33.3%)
	Relapsed	11 (36.6%)
LGSOC	Newly diagnosed	2 (6.7%)
	Relapsed	5 (16.7%)
Other		2 (6.7%)
LUNG		13 (24.6%)
NSCLC	Newly diagnosed	8 (61.5%)
	Relapsed	4 (30.8%)
Secondary malignant neoplasm of pleura		1 (7.7%)
BREAST		4 (7.5%)
PANCREAS		2 (3.8%)
MANTLE CELL LYMPHOMA		4 (7.5%)

B) Indication-level functional response



'617 Driven Inhibition:

Lower immune cell mediated toxicity compared to other CDK7 clinical candidates

C) Overall patient cohort

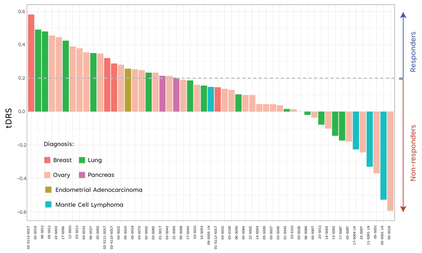
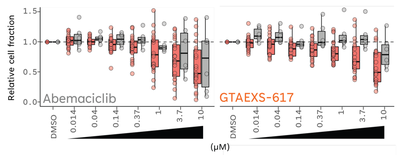


Figure 1: (A) Global cohort characteristics. HG/LG-SOC: High-grade/low-grade serous ovarian carcinoma; NSCLC: Non-small-cell lung cancer. **(B1)** Examples of patient response profiles: drug toxicity is normalised to DMSO control. Curve smoothness and slope determines the total drug response score (tDRS) over concentrations shown in Figure 2.[1–3] **(B2)** Intra-tumoural immune cell specific toxicity of '617 (immune tDRS). CT-7001 and SY-5609: CDK7i; abemaciclib: CDK4/6i. **(C)** Overall cancer cohort '617 cancer specific toxicity.

Figure 2: Sub-cohort level '617 effect specificities

A) Subtypes and/or treatment status influence on functional response



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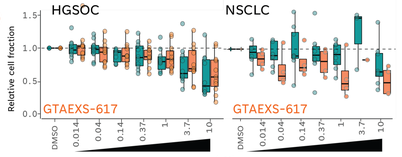


CDK7 Inhibition:

- HGSOC subtype is associated with highest drug response score
- Limited LGSOC CDK7i sensitivity
- Lung cancer anti-PD1 refractory patients presented slightly higher '617 tDRS

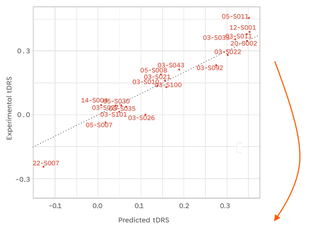
Subtype: HGSOC LGSOC

Treat. status: ND R/R

Figure 2: (A) CDK4/6 inhibitor (abemaciclib) and CDK7 inhibitor sensitivities in 72h-treated ovarian cancer patient cohort according to pathology subtype. **(B)** Treatment status influence in ovarian and lung cancer cohort. ND: Newly diagnosed; R/R: Relapsed.

Figure 3: Predicting '617 response using tumour transcriptome profiling

A) Using AI to establish '617 response predictor algorithm with matched functional response/ transcript profiling in ovarian samples cohort



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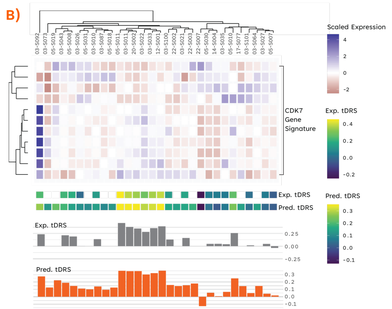


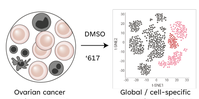
C) Predicting drug response in prospectively sequenced ovarian samples

Sample ID	Exp. tDRS	Pred. tDRS
Sample 01	0.446	0.179
Sample 02	0.254	0.222
Sample 03	0.248	0.125
Sample 04	0.099	0.146
Sample 05	-0.179	0.094
Sample 06	-0.370	0.101
Sample 07	-0.594	0.124

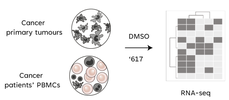
Figure 3: (A) Modelling tumour intrinsic RNA features predictive of '617 tDRS. **(B)** Transcript gene signature used in predictive modelling. **(C)** Applying the predictor geneset identified in **(A and B)** to prospectively predict '617 tDRS and enrich for responders. The model will be evaluated across multiple indications, alongside the inclusion of genomic features to further increase robustness.

Figure 4: Identifying response PD biomarker using cancer patient PBMCs, scRNA and tumour transcriptome after '617 exposure

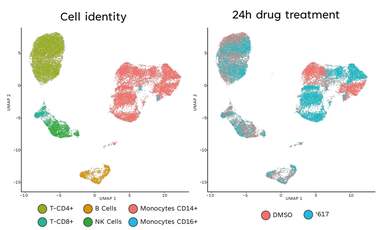
A1) PD biomarker transcript identification



A2) Transcript candidate validation



B) Effect of '617 on single cells in patient samples



C) Identification of PD (pharmacodynamic) biomarker candidates

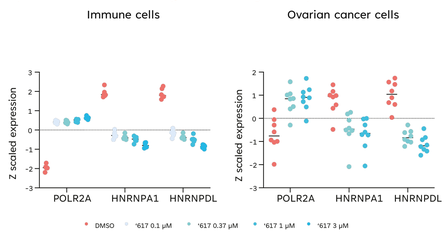


Figure 4: (A) *Ex vivo* exposure of primary models for PD biomarker discovery. **(B)** Single cell analysis of ovarian cancer patient PBMCs upon '617 treatment (24h and 0.37 and 1.0 μM stimulation aggregated together) showing CD14 clustering changes. **(C)** Validation of identified PD gene candidates in immune (N=6) and ovarian (N=8) primary models exposed to '617 for 24 hours from Figure 4B using RNA sequencing. Alongside previously reported POLR2A, identification of other gene candidates.[4]

DISCUSSION

We demonstrated '617 to induce cancer cell specific death in primary cancer samples, while having reduced intra-tumoral immune cell toxicity. Combining single cell quantification of drug action and omics data, we revealed a diversity of response in primary samples and generated a transcriptomic-based proof of concept algorithm in ovarian cancer to enrich for '617 responders. We aim to further integrate patients' specific genomic data to refine our predictive algorithm while expanding it to other indications.

Pharmacodynamic biomarkers, both previously reported and potentially novel, were revealed in the cancer and immune compartment, where non-invasive detection could be possible.

CONCLUSIONS

Here, we describe an approach enabling the rapid assessment of new therapies in primary human disease samples containing host immune cells. Taken together with functional data this can be used to define a patient stratification signature and PD markers.

By combining AI-based patient tissue analysis and transcriptomic data, we identified both a PD marker and gene signature specific to CDK7 and the drug candidate '617, which may distinguish patients that will optimally respond to therapy.

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