Abstract No. 35265

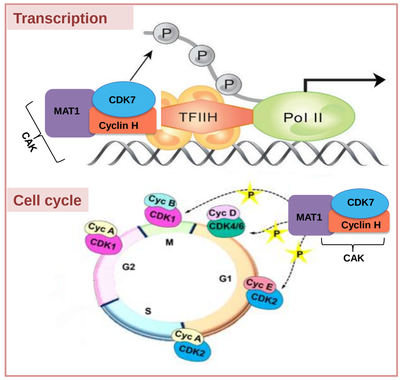
Identifying Sensitive Patient Populations for CDK7 Inhibitors Using Cell Panel Screens and Bioinformatic Approaches

Keisha Hearn, Maria Ahn, Luke Bevan, Jessica Brothwood, Charlotte East, Anna Esteve-Arenys, Lynsey Fazal, Christopher Hindley, Sabrina James, Justyna Kucia-Tran, John Lyons, Joanne Munck, Harpreet Saini, Mathieu Unbekandt, Dhaval Varshney, Steve Wagner, Andrew Woodhead and Nicola Wallis

Astex Pharmaceuticals, 436 Cambridge Science Park, Milton Road, Cambridge, CB4 0QA, United Kingdom

INTRODUCTION

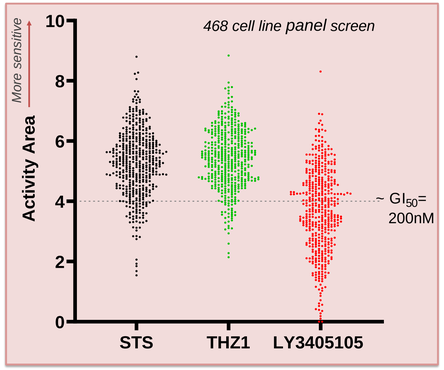
Cyclin-dependent kinase 7 (CDK7) is an attractive oncology target with several inhibitors being tested in clinical trials owing to its essential roles in cell cycle and transcription. Given that dysregulation of these processes promote tumorigenesis and tumor growth, preclinical data shows that such agents could have utility across a range of tumor types particularly those driven by defects in the regulation of cell cycle and transcriptional processes. Consequently, patient populations are broad and often lack well-defined patient stratification. To identify specific cancers with greater dependence on CDK7 activity, we carried out a cell line panel screen coupled with bioinformatic analysis of association of drug sensitivity to molecular features



CDK7 dual biological function:
i) Regulates transcription by phosphorylating RNA Pol II (Ser5)
ii) CDK-activating kinase (CAK) activity directly regulates cell cycle

2. BROAD RANGE OF SENSITIVITIES TO SELECTIVE CDK7 INHIBITION

- Two CDK7 inhibitors (THZ1[1] and LY3405105[2]) and the non-selective kinase inhibitor staurosporine were profiled across a panel of 468 human cancer cell lines with varied genetic backgrounds
- Activity area (AA) was used to define drug responses and calculated as the area over the dose-response curve
- THZ1 and the control staurosporine had a similar, pan-active profile across cell lines compared to LY3405105 which had a more selective effect
- Bioinformatic approaches used to explore tumor sensitivities to CDK7 inhibition



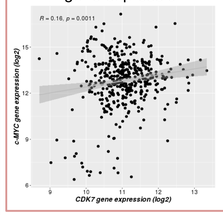
Proliferation measured using 96 hr CellTiter-Glo® assay

3. GLOBAL c-MYC SIGNATURE CONFERS SENSITIVITY TO CDK7 INHIBITION

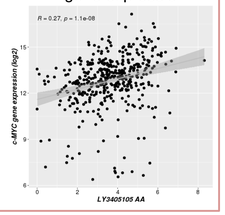
Multi-omics features of cell lines (DepMap) were used to define molecular features associated with drug response (sensitivity defined as activity area (AA))

All cell lines

CDK7 gene expression as a function of c-MYC gene expression

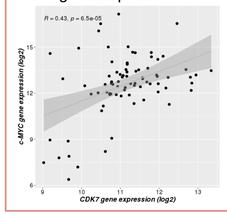


LY3405105 AA as a function of c-MYC gene expression

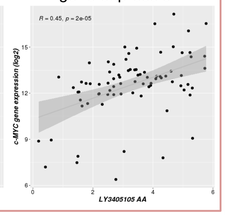


Lung cell lines only

CDK7 gene expression as a function of c-MYC gene expression



LY3405105 AA as a function of c-MYC gene expression



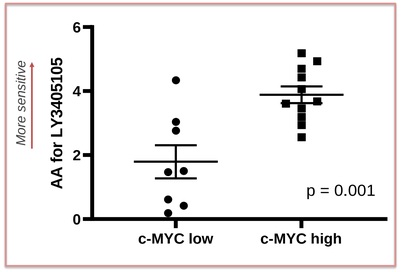
Bioinformatics analysis:

- A c-MYC expression signature was found across the entire cell panel and had the highest correlation in lung cancer (SCLC & NSCLC) cell lines

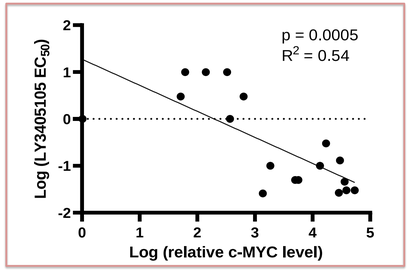
4. c-MYC SIGNATURE WAS HIGHLY CORRELATED IN SCLC

SCLC cell lines

LY3405105 sensitivity as a function of c-MYC gene expression



Significant correlation between c-MYC gene expression and LY3405105 sensitivity (AA) in all SCLC cell lines from the cell panel screen

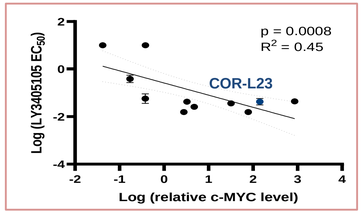


Significant correlation between c-MYC gene expression and LY3405105 sensitivity (EC_{50}) confirmed across an independent panel of 18 SCLC cell lines with varying levels of c-MYC

5. c-MYC SIGNATURE WAS HIGHLY CORRELATED IN NSCLC

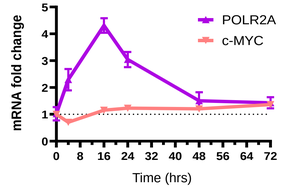
NSCLC cell lines

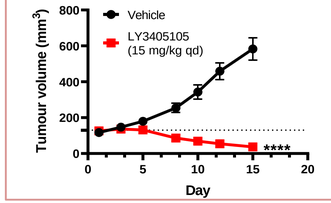
LY3405105 sensitivity as a function of c-MYC gene expression



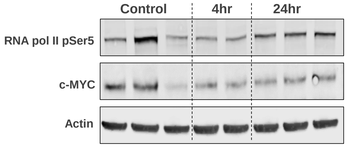
Significant correlation between c-MYC gene expression and LY3405105 sensitivity (EC_{50}) across an independent panel of 11 NSCLC cell lines with varying levels of c-MYC

COR-L23 tumor xenografts





LY3405105 treatment led to pathway modulation downstream of CDK7 and significant anti-tumor activity



Mice bearing COR-L23 tumor xenografts were dosed orally with 15-20 mg/kg of LY3405105 at time points and schedules indicated. Tumors were collected at indicated timepoints and protein levels assessed by RT-qPCR and western blotting.

*Anti-tumor activity; each data point represents mean ± SEM (n ≥ 7). **** p-value < 0.0001 vs vehicle by 2-way ANOVA (Mixed-effects model). Compound was well tolerated*

SUMMARY AND CONCLUSIONS

- Cell panel drug screening coupled with bioinformatic analyses was used to identify potentially sensitive patient populations for CDK7 inhibitors
- We identified a c-MYC expression signature which confers sensitivity to CDK7 inhibition and was highly correlated in lung cancer cell lines
- Using independent panels of cell lines with varying c-MYC levels, we confirmed these findings in vitro and the results were further validated in vivo where we observed pathway modulation and partial tumor regressions

REFERENCES:
1. Kwiatkowski et al., 2014. Nature, 511(7511): 616–620
2. Garralda et al., 2023. The Oncologist, oyad215

astex pharmaceuticals