Predicting MCL1 inhibitor sensitivity in large cell line panels using a gene expression signature

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**INTRODUCTION**

MCL1, an anti-apoptotic member of the BCL-2 family of proteins, is a key regulator of cancer cell survival and a known resistance factor to anti-cancer drugs, making it a highly desirable target for therapeutic intervention. Recently several MCL1 inhibitors have entered Phase I clinical development. Data derived from large cancer cell line panels suggest that cell lines of hematopoietic origin are more broadly sensitive to MCL1 inhibition than cell lines derived from solid tumor types. Therefore in particular for the therapy of solid tumor patients with an MCL1 inhibitor, a patient selection biomarker would be highly desirable.

**METHODS**

3 solid tumor cell line panels from the Massachusetts General Hospital (682 cell lines), the CRC Brain Tumor Panel (1,430 cell lines), and the CRISPR/Cas9 screens (672 cell lines) were tested to the MCL1 inhibitor (Avana, Boehringer). Genes are available on https://bonsai.ingelheim.com.

**RESULTS CELL LINES**

- **Gene expression data of these cell lines are based on Illumina TruSeq RNA-seq from either the Cancer Cell Line Encyclopedia or internal sequencing runs. RNA isolation, library preparation, and sequencing was performed as described in ref. 3. Data processing is based on an adapted ENCODE RNA-seq pipeline (GRCh38) and gene annotations from Ensembl 86.
  - Differential gene expression of RNA-seq data is based on a modified t-test. Genes that were differentially expressed (log2FC ≥ 1) between the two cell lines were then identified as being significantly differentially expressed (p-value < 0.05, adjusted for multiple testing)

**RESULTS TISSUES**

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**REFERENCES**

2. Meyers et al., Computational combination of copy number effect improves specificity of CRISPR-Cas9 essentiality screens in cancer cells. Nature Biotechnology 2017;
3. Gerlach et al., The novel BET bromodomain inhibitor BI 855995 represses super-enhancer-associated transcription and synergizes with CDK9 inhibition in AML. Oncogene 2018;
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8. The Genotype-Tissue Expression (GTEX) project: https://gtexportal.org

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**SUMMARY**

Published in vitro data using various MCL1 inhibitors, RNAi or CRISPR/Cas9, both showed that human tumor cell lines with low BCL-XL gene expression are most sensitive to MCL1 inhibition, down-regulation or inactivation. We demonstrate that by using the gene expression data of additional five genes (including the MCL1 binding partner BAK1) to BCL-XL, a supervised learning predictor reaching a sensitivity of above 90% correctly classified solid tumor cell lines. An additional predictor based on all available cell line data was applied to either tumor samples, adjacent normal tissues or normal tissue samples from TCGA and GTEx, showing that many normal tissue samples are categorized as being sensitive. Moreover, solid tumor samples were used to build solid tumor cell line predictors being able to be broadly sensitive to MCL1 inhibition, in some tumor types reaching over 90% of all cases. In summary, our work describes the translational challenges when applying solid tumor cell line predictors on tumor samples and thus comprehensive studies are required.

**CONCLUSIONS**

- An mRNA screen, a CRISPR/Cas9 screen and a pharmacological screen of large solid tumor-derived cancer cell lines targeting MCL1 lead to a consistent classification into sensitive and resistant samples to growth inhibition
- Cell lines with low BCL-XL (BCL-XL) gene expression are mostly sensitive to MCL1 inhibition
- A supervised learning predictor using the gene expression of BCL2L1 (BCL-XL), of the MCL1 binding partner BAK1 and of four additional genes can reliably predict sensitivity and resistance to MCL1 inhibition in cancer cell lines
- However, the application of this cell line predictor to develop patient stratification strategies for clinical trial design suffers from clear limitations.

**REFERENCES**

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