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## **Systematic identification of rational drug combinations in Burkitt lymphoma cell lines**

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Burkitt lymphoma (BL) is a highly aggressive non-Hodgkin lymphoma originating from the dark zone germinal-centre B cells. It is characterized by a translocation of *MYC* oncogene, which cooperates with the activation of the phosphoinositide 3-kinase (PI3K) pathway in lymphomagenesis. As the mutational landscape of BL becomes clearer, the possibility of targeted therapies as alternative treatment options arises. Although younger patients have favourable outcomes with chemoimmunotherapy, there is a need for alternative and less toxic regimens for elderly, immunosuppressed or relapsed patients.

In this study, pharmacological profiling of cell lines derived from haematological malignancies with a focus on BL was performed using a library of 32 drugs. Based on those results, a parallel approach was used to evaluate 96 drug combinations in 18 BL cell lines. Due to the role of tonic B-cell receptor (BCR) signalling to PI3K and *MYC* overexpression in BL, Bruton's tyrosin kinase (BTK), PI3K and bromodomain and extraterminal motif family (BET) inhibitors were chosen as combination partners. Drug response phenotypes of cell lines were also compared to acute lymphoblastic leukaemia (ALL) primary patient samples.

Pharmacological profiling of BL cell lines revealed two distinct groups, which differed in their response to kinase inhibitors, including BTK, SYK, PI3K, AKT and mTOR inhibitors. This work implies that a subset of BL may benefit of treatment with drugs inhibiting BTK, SYK or the PI3K/AKT/mTOR pathway and underscores the necessity of assessment of those drugs in clinical trials. Cell line specific sensitivities were observed, i.e. to Bcl-2 inhibitor driven by overexpression of Bcl-2 protein or to Bcr-Abl inhibitors in chronic myeloid leukaemia (CML) line. Furthermore, it was shown that cell lines faithfully mimic drug response phenotype of primary ALL cells and are hence a reliable model for pharmacological profiling.

This combination study identified numerous cooperative drug interactions. The strongest synergy was found between CDK 2,7,9 inhibitor SNS-032 and a novel BET inhibitor (BETi) OTX015, as well as numerous inhibitors of the PI3K/AKT/mTOR pathway and BETi. A small subset of BL lines showed synergy between BCR inhibition by ibrutinib and PI3K inhibition by idelalisib. The same sample group showed cooperative drug interaction between BTK inhibition by ibrutinib and BETi by OTX015.

To conclude, a robust and comprehensive tool for pharmacological profiling of cell lines was established. The systematic approach allowed the identification of numerous drugs as well as drug combinations that can be potentially beneficial for BL patients. The study underscores the urgency of their evaluation in clinical trials and translation into the clinic.