

# Phenotype-based drug screening in primary ovarian carcinoma cultures identifies intracellular iron depletion as a promising strategy for cancer treatment.

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## Source

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## Abstract

Primary cultures of patient tumor cells (PCPTC) have been used for prediction of diagnosis-specific activity and individual patient response to anticancer drugs, but have not been utilized as a model for identification of novel drugs in high throughput screening. In the present study, ovarian carcinoma cells from three patients were tested in response to a library of 3000 chemically diverse compounds. Eight hits were retrieved after counter screening using normal epithelial cells, and one of the two structurally related hit compounds was selected for further preclinical evaluation. This compound, designated VLX 50, demonstrated a broad spectrum of activity when tested in a panel of PCPTCs representing different forms of leukemia and solid tumors and displayed a high tumor to normal cell activity. VLX 50 induced delayed cell death with some features of classical apoptosis. Significant *in vivo* activity was confirmed on primary cultures of human ovarian carcinoma cells in mice using the hollow fiber model. Mechanistic exploration was performed using gene expression analysis of drug exposed tumor cells to generate a drug-specific signature. This query signature was analyzed using the Gene Set Enrichment Analysis and the Connectivity Map database. Strong connections to hypoxia inducible factor 1 and iron chelators were retrieved. The mechanistic hypothesis of intracellular iron depletion leading to hypoxia signaling was confirmed by a series of experiments. The results indicate the feasibility of using PCPTC for cancer drug screening and that intracellular iron depletion could be a potentially important strategy for cancer therapy.