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Targeting autophagy by small molecule inhibitors of vacuolar protein sorting 34 (Vps34) improves the sensitivity of breast cancer cells to Sunitinib

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Resistance to chemotherapy is a challenging problem for treatment of cancer patients and autophagy has been shown to mediate development of resistance. In this study we systematically screened a library of 306 known anti-cancer drugs for their ability to induce autophagy using a cell-based assay. 114 of the drugs were classified as autophagy inducers; for 16 drugs, the cytotoxicity was potentiated by siRNA-mediated knock-down of Atg7 and Vps34. These drugs were further evaluated in breast cancer cell lines for autophagy induction, and two tyrosine kinase inhibitors, Sunitinib and Erlotinib, were selected for further studies. For the pharmacological inhibition of autophagy, we have characterized here a novel highly potent selective inhibitor of Vps34, SB02024. SB02024 blocked autophagy *in vitro* and reduced xenograft growth of two breast cancer cell lines, MDA-MB-231 and MCF-7, *in vivo*. Vps34 inhibitor significantly potentiated cytotoxicity of Sunitinib and Erlotinib in MCF-7 and MDA-MB-231 *in vitro* in monolayer cultures and when grown as multicellular spheroids. Our data suggests that inhibition of autophagy significantly improves sensitivity to Sunitinib and Erlotinib and that Vps34 is a promising therapeutic target for combination strategies in breast cancer.