Autophagy Inhibitors

These potent autophagy inhibitors show strong promise for significantly reducing tumor survival and progression.

Background

Autophagy is a cellular catabolic process which generates internal nutrient pools by targeting portions of cytosol to the lysosome for degradation. In times of stress, autophagy is activated to produce energy, clear damaged organelles, and delay or even prevent cell death. Autophagy is critical for tumor survival and progression, permitting cells to adapt to stressors such as hypoxia and chemotherapy. Additionally, oncogenic transformation can contribute to autophagy activation; specific oncogenes and tumor suppressors enhance autophagy activity, promoting cell survival in many tumor types including lung cancer and melanoma. Further evidence shows that autophagy permits cell adaption to metabolic stress and promotes tumor metastasis. Altogether, these findings support the rationale to inhibit autophagy as a therapeutic intervention in cancer; oncogene-driven tumors should be particularly susceptible to this strategy.

Chloroquine (CQ), an acidotropic compound that disrupts lysosomal function, inhibits autophagy and is already safely used in humans for treating malaria. Unfortunately, CQ requires relatively high concentrations to inhibit autophagy, making it sub-optimal as a cancer therapeutic. Thus, to successfully target autophagy in cancer, more potent compounds are needed.

Technology

Investigators at Van Andel Research Institute (VARI) and the Translational Genomics Research Institute (TGen) collaborated to develop several novel, potent autophagy inhibitors. These compounds exhibit substantially improved efficacy as demonstrated by chemical screening of CQ-related compounds and subsequent structure-activity relationship (SAR) approaches.

![Figure 1](image1.png)

**Figure 1:** VATG-27 and VATG-32 show greater autophagy inhibition than chloroquine. 

A. Autophagy plays a crucial role in tumorigenesis and chemoresistance promotes tumor cell survival. B. This fluorescent intensity profile shows the effects of autophagy inhibition on sarcoma cells; the effects can be followed over time. In this image, the nucleus (blue), endosomes (green), and lysosomes (red) are shown. VATG-27 and VATG-32 inhibit autophagy by de-acidifying lysosomes so they can no longer digest cellular materials, eventually resulting in cell death or therapeutic sensitization.

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Figure 2: VATG-27 and VATG-32 show greater autophagy inhibition than chloroquine. A, U2OS-tfLC3 cells were treated for 3 h with chloroquine, VATG-27, or VATG-32 at the indicated concentrations, fixed, and imaged at 60x magnifications. In these images, GFP-LC3 (green), RFP-LC3 (red), and Hoechst (blue; nuclei) are shown. Scale bars: 20 μm. Insets are 2.5x magnifications of boxed regions. B, Cell viability after 48 hours of treatment (+) with chloroquine, quinacrine, VATG-27, or VATG-32; and C, Flow cytometry analysis of cleaved caspase-3 after treatment with chloroquine, quinacrine, VATG-27, and VATG-32.

Insights

Initial studies investigating CQ analogs, VATG-27 and VATG-32, in cancer treatment focused on their ability to induce cell death as single agents. Even though cytotoxic compounds are valuable, potent autophagy inhibition alone does not necessarily elicit cytotoxic effects. Our novel compounds demonstrate that potent autophagy inhibition can be accomplished while being relatively well-tolerated by cells (i.e., VATG-32). These potent autophagy inhibitors provide an opportunity for developing adjuvant treatment strategies, effectively blocking autophagy-mediated cancer cell survival without significantly increasing toxicity as a single agent. These types of compounds have great potential for further sensitizing cancer cells to the latest anticancer therapeutics.

References:
2. Goodall ML et al. (2014) “Development of potent autophagy inhibitors that sensitize oncogenic BRAF V600E mutant melanoma tumor cells to vemurafenib.” Autophagy