Vorinostat

- Interrogation of macrophage-related prognostic signatures reveals a potential immune-mediated therapy strategy by histone deacetylase inhibition in glioma
- A PANoptosis-Based Signature for Survival and Immune Predication in Glioblastoma Multiforme
- Reduced EZH1/2 expression in imipridone-treated cells correlates with synergy following combinations with EZH1/2 or HDAC inhibitors in diffuse glioma and other tumors
- Generation and validation of a novel multitarget small molecule in glioblastoma
- Vorinostat attenuates UVB-induced skin senescence by modulating NF-kappaB and mTOR signaling pathways
- Characterization of an Enhancer RNA Signature Reveals Treatment Strategies for Improving Immunotherapy Efficacy in Cancer
- Hepatocellular Carcinoma Cells in Humans Exhibit Resistance to Suberoylanilide Hydroxamic Acid (SAHA) Owing to the Diminished Level of Hsa-miR-125a-5p
- Bioinspired black phosphorus delivers histone deacetylase inhibitor-induced synergistic therapy for lung cancer

---

Vorinostat, is a histone deacetylase inhibitor, given concurrently with stereotactic radiosurgery (SRS) for non-small cell lung cancer intracranial metastases treatment.

Excessive exposure to ultraviolet B (UVB) radiation induces oxidative stress and inflammatory responses, accelerating the senescence process of skin cells. Vorinostat (SAHA), a histone deacetylase inhibitor (HDACi), is typically administered to patients with peripheral T-cell lymphoma, cutaneous T-cell lymphoma, or multiple myeloma. However, its effect on UVB-induced skin photoaging remains unclear.

Dai et al. used UVB to induce senescence in human immortalized keratinocyte cell line (HaCaT cells) and skin photoaging in Balb/c mice to investigate the potential of SAHA in mitigating photoaging. First, we established a UVB-induced photoaging model in HaCaT cells. We observed that UVB exposure significantly upregulated the activity of senescence-associated β-galactosidase, p16, p21, IL-1β, IL-6, and matrix metalloproteinases [collagenase (MMP-1), matrix metalloproteinase-3 (MMP-3), and gelatinase (MMP-9)]. Supplementation with SAHA effectively alleviated cellular senescence in HaCaT cells. Next, we used UVB to induce photoaging in Balb/c mouse skin. The study demonstrated that UVB markedly caused skin senescence in Balb/c mice, while SAHA effectively mitigated the changes induced by UVB irradiation. Mechanistically, we found that UVB activated the mammalian target of rapamycin (mTOR) and nuclear factor-κB (NF-κB) signaling pathways, whereas SAHA inhibited the upregulation of both mTOR and NF-κB. In summary, these findings suggest that SAHA may protect against UVB-induced cellular senescence and skin photoaging by inhibiting the mTOR and NF-κB signaling pathways. Therefore, SAHA could be a potential anti-senescence agent for mitigating skin photoaging [1)].

The maximum tolerated dose (MTD) of vorinostat with concurrent SRS was established as 400 mg.

Although no dose-limiting toxicity (DLT) were observed, 5 patients withdrew before completing the treatment course, a result that emphasizes the need for supportive care during vorinostat administration. There were no local failures. A larger, randomized trial may evaluate both the tolerability and potential local control benefit of vorinostat concurrent with SRS for brain metastases [2)].

Premkumar et al. demonstrated that proteasome inhibitors, such as bortezomib, dramatically sensitized highly resistant glioma cells to apoptosis induction, suggesting that proteasomal inhibition may be a promising combination strategy for glioma therapeutics.

They examined whether bortezomib could enhance response to HDAC inhibition in glioma cells. Although primary cells from glioblastoma multiforme (GBM) patients and established glioma cell lines did not show significant induction of apoptosis with vorinostat treatment alone, the combination of vorinostat plus bortezomib significantly enhanced apoptosis. The enhanced efficacy was due to proapoptotic mitochondrial injury and increased generation of reactive oxygen species. Our results also revealed that combination of bortezomib with vorinostat enhanced apoptosis by increasing Mcl-1 cleavage, Noxa upregulation, Bak and Bax activation, and cytochrome c release. Further downregulation of Mcl-1 using shRNA enhanced cell killing by the bortezomib/vorinostat combination. Vorinostat induced a rapid and sustained phosphorylation of histone H2AX in primary GBM and T98G cells, and this effect was significantly enhanced by co-administration of bortezomib. Vorinostat/bortezomib combination also induced Rad51 downregulation, which plays an important role in the synergistic enhancement of DNA damage and apoptosis. The significantly enhanced antitumor activity that results from the combination of bortezomib and HDACIs offers promise as a novel treatment for glioma patients [3)].

Indications

FDA-Approved Indication

Cutaneous T-cell lymphoma (CTCL):

Specifically for **patients with progressive, persistent, or recurrent CTCL** who have failed at least two prior systemic therapies.

Investigational / Off-label Uses (in clinical trials or research)

Vorinostat is being studied in various **solid and hematologic malignancies**, including:

- **Non-Hodgkin lymphoma (NHL)**

- **Multiple myeloma**

- **Acute myeloid leukemia (AML)**

- **Chronic lymphocytic leukemia (CLL)**

- **Glioblastoma**

- **Breast cancer**

- **Prostate cancer**

- **Non-small cell lung cancer (NSCLC)**

- **Pancreatic cancer**

It is often evaluated in **combination with other chemotherapeutic agents, radiation therapy, or immunotherapy**, given its ability to affect gene expression and sensitize cancer cells.

Vorinostat for Intracerebral Hemorrhage

see Vorinostat for Intracerebral Hemorrhage.

1)
Dai Q, Wang Z, Wang X, Lian W, Ge Y, Song S, Li F, Zhao B, Li L, Wang X, Zhou M, Cheng J. Vorinostat attenuates UVB-induced skin senescence by modulating NF-κB and mTOR signaling pathways. Sci Rep. 2025 Mar 29;15(1):10905. doi: 10.1038/s41598-025-95624-4. PMID: 40158057.
2)
Choi CYH, Wakelee HA, Neal JW, Pinder-Schenck MC, Yu HM, Chang SD, Adler JR, Modlin LA, Harsh GR, Soltys SG. Vorinostat and Concurrent Stereotactic Radiosurgery for Non-Small Cell Lung Cancer Brain Metastases: A Phase 1 Dose Escalation Trial. Int J Radiat Oncol Biol Phys. 2017 Sep 1;99(1):16-21. doi: 10.1016/j.ijrobp.2017.04.041. Epub 2017 May 6. PubMed PMID: 28816142.
3)
Premkumar DR, Jane EP, Agostino NR, DiDomenico JD, Pollack IF. Bortezomib-induced sensitization of malignant human glioma cells to vorinostat-induced apoptosis depends on reactive oxygen species production, mitochondrial dysfunction, Noxa upregulation, Mcl-1 cleavage, and DNA damage. Mol Carcinog. 2013 Feb;52(2):118-33. doi: 10.1002/mc.21835. Epub 2011 Nov 15. PubMed PMID: 22086447; PubMed Central PMCID: PMC4068609.