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LETTER

# RET Inhibitor SPP86 Is a Potential Candidate for the Clinical Treatment of Cutaneous Melanoma [Letter]

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## Dear editor

We recently read with great interest the article "RET Inhibitor SPP86 Triggers Apoptosis and Activates the DNA Damage Response Through the Suppression of Autophagy and the PI3KAKT Signaling Pathway in Melanoma Cells" by Zhang et al,[1] published in your journal. This study presents that SPP86 exerts anti-tumor effects through suppressing the autophagy and PI3K/AKT signaling pathway in two melanoma cell lines, indicating that it was a promising potential drug for the treatment of skin malignant melanoma.

The research showed that SPP86, a RET inhibitor, could decrease cell viability, proliferation, and clone-forming ability but induce apoptosis and DNA damage in melanoma A375 and A2058 cell lines. Compared with the control group, cleaved caspase-3 and PARP1 were measured and showed a dose-dependent increase in melanoma cell lines treated with SPP86, demonstrating that the break of double-strand DNA. Further work identified that the inhibition of autophagy (Baf A1) or activation of PI3K/AKT signaling (YS-49) rescued the impact of SPP86 by CCK-8 assay, TUNEL assay, and Western blot.

However, there are still some limitations in this project. Firstly, the lack of in vivo experiments makes the results a little bit less convincing. The researchers are supposed to repeat the related experiments on the ultraviolet-induced melanoma mouse model, DMBA or TBA-induced melanoma mouse model, transplantation mouse model and transgenic mouse model.[2] Secondly, PARP1 plays a key role in the DNA damage and cell death of many diseases and the theory of synthetic lethality has been proposed based on the effect of PARP1 in cancers.[3] Olaparib, the first PARP1 inhibitor approved by the FDA, demonstrates great therapeutic effect and clinical applications on several cancers.[4] Consequently, synthetic lethality-based therapies can be applied in melanoma cell lines and mouse models. Lastly, future efforts should focus on the long-term efficacy and safety of the SPP86, which is pivotal for the clinical therapeutic effect on patients.

Collectively, the work by Zhang et al provides valuable insights into the treatment potential of SPP86 on skin melanoma. However, the in vivo evidence and synthetic lethality-based therapies warrant further investigation and exploration.

## Disclosure

The authors report no conflicts of interest in this communication.

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