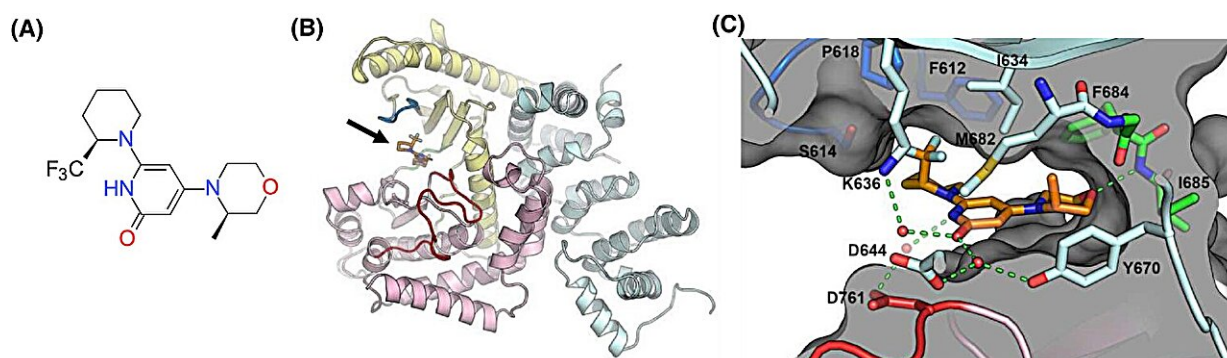


A new hope in immunotherapy against cancer

April 3 2024



Identification of SB02024 as a potent and selective inhibitor of VPS34. (A) Chemical structure of SB02024. (B) Cartoon representation of the structure of complex between VPS34 Δ C2 and SB02024. The N-, C-lobes, and helical domains of VPS34 Δ C2 are colored in yellow, pink, and light cyan, respectively. The hinge region, P-loop, and activation loop are colored in green, blue, and red, respectively. SB02024 is displayed as sticks with its carbon atoms colored orange. SB02024 location in VPS34 Δ C2 active site is pinpointed by a black arrow. (C) SB02024 binding-site with color code as in panel B. Credit: *Molecular Oncology* (2024). DOI: 10.1002/1878-0261.13619

In a new study [published](#) in *Molecular Oncology*, researchers have discovered a novel mechanism to enhance the body's immune response to tumors.

The study is a result of collaboration between Sprint Bioscience, Karolinska institutet, the Luxembourg Institute of Health and Deciphera Pharmaceuticals, and was included as a manuscript in Yasmin Yu's Ph.D. thesis at the Department of Oncology-Pathology in 2021.

A dual attack on cancer's defenses

Cancer cells are notorious for creating an immunosuppressive environment that shields them from the body's natural defenses. Inhibition of cellular recycling mechanism—autophagy—by targeting selectively a key protein VPS34 leads to an increase in specific chemokines, CCL5 and CXCL10, which act like beacons, guiding [immune cells](#) to the tumor site.

The new study demonstrates that it is the triggering of a type I Interferon pathway through cGAS-STING activation that is the underlying molecular mechanism. When combined with STING agonists, VPS34 inhibition further increased cytokine production and anti-tumor effects in a melanoma mouse model. Thus, an activation of a pro-inflammatory response and an enhanced recruitment of immune cells not only hampers [tumor growth](#) but can also improve the effectiveness of an existing immunotherapy.

Understanding of the molecular mechanisms behind the action of VPS34 inhibition and promising results of combination with immune therapy in mouse models may pave the way for clinical trials in humans.

Angelo De Milito, Ph.D., director of tumor biology and therapeutics at Sprint Bioscience and associated with the Department of Oncology-Pathology, says, "This publication as well as the work performed by Yasmin Yu during her doctoral studies result from a close, stimulating

and productive collaboration between industrial and academic partners and show how such collaborative projects may have a positive impact in terms of education, scientific knowledge and innovation.

"Such advancement in understanding the role of VPS34 in modulating type I interferon signaling provides a scientific rationale to investigate combination therapies with different classes of immune-activating agents."

More information: Yasmin Yu et al, Combining VPS34 inhibitors with STING agonists enhances type I interferon signaling and anti-tumor efficacy, *Molecular Oncology* (2024). [DOI: 10.1002/1878-0261.13619](https://doi.org/10.1002/1878-0261.13619)

Provided by Karolinska Institutet

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