ENHANCED THERAPEUTIC TREATMENT OF CANCER THROUGH SYNERGISTIC INHIBITION OF SHIP2 AND PLK1

KEYWORDS

- PLK1
- SHIP2
- Small molecules inhibitors
- Synergistic Combination
- Cancer

Collaboration type
Collaborative R&D (pre-clinical, early clinical)
Licensing

IP status
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THE TECHNOLOGY IN A NUTSHELL

New synergistic combinations of small molecules PLK1 inhibitors and SHIP2 inhibitors as anti-cancer drugs.

STATE OF THE ART

Polo-like kinase I (PLK1), a cell cycle regulating kinase, is a relevant target for the development of cancer drugs. Although PLK1 inhibitors, such as volasertib, are well-tolerated and present favorable pharmacokinetic profiles, their clinical success remains still limited. PLK1-based combination therapies have therefore been the focus of intensive research. While such combined therapies have achieved different degrees of success in preclinical and clinical settings, there is a pressing need to identify and validate novel biologically informed co-targets for PLK1-based combinatorial therapies and to develop synergistic combinations between PLK1 inhibitors and other agents for enhanced cancer treatment.

THE INVENTION

The phosphoinositide 3-kinase (PI3K)/mTOR/AKT pathway ranks as the most frequently activated pathway in human cancer. Given the critical role of the PI3K/AKT pathway in cancer progression, multiple inhibitors have been designed to selectively dampen its activation in cancer cells. However, due to the pathway's ubiquity and its influence on vital physiological functions, these inhibitors elicit side effects that can compromise treatment efficacy. In the PI3K pathway, PI 5-phosphatases, and particularly SH2-containing 5' inositol phosphates 1 and 2 (SHIP1/2) emerge as pivotal regulating enzymes. Leveraging SHIP2 knockdown *in vitro* enabled the inventor to show the regulatory influence of SHIP2 expression on esophageal cancer cells survival and adhesion. In addition, pharmacological inhibition of SHIP2 phosphatase activity effectively suppresses esophageal Squamous Cell Carcinoma (eSCC) cell survival both *in vitro* and *in vivo*.

The inventors further demonstrated that inhibition of both SHIP2 and PLK1 results in a synergistic effect on eSCC cells as well as cell lines of other types of cancer. Combinations of a SH2 domain-containing inositol 5'-phosphatase 2 (SHIP2) inhibitor and a Polo-like kinase I (PLK1) inhibitor provides therefore a new strategy for enhanced combined treatments of cancers, and in particular cancers overexpressing SHIP2 due to INPPL1 amplification.

KEY ADVANTAGES OF THE TECHNOLOGY

- New synergistic combination treatment against cancer based on PLK1 and SHIP2 inhibitors.
- *in vitro* and *in vivo* efficacy demonstrated in pre-clinical studies.

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TECHNOLOGY READINESS LEVEL

1 2 **3** 4 5 6 7 8 9

TRL-3 Proof of concept: synergistic inhibition of esophageal squamous carcinoma and other cancer cell lines *in vitro* and first *in vivo* results on xenotransplanted mice demonstrating potential for development of enhanced combined treatment of cancer.

LABORATORY AND INVENTOR

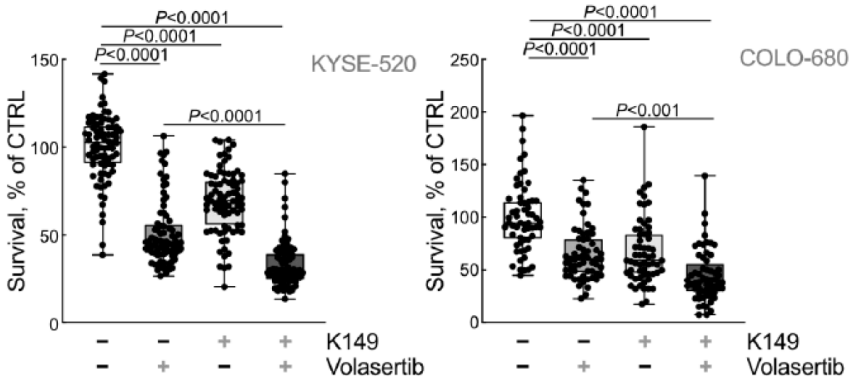
The Institute of Interdisciplinary Research in human and molecular Biology (IRIBHM) gathers 130 researchers and technicians applying interdisciplinary approaches to the study medically relevant topics encompassing signal transduction, development, neuroscience, and cancer, using cell and molecular biology approaches. Staff researchers include physicians, physicists, bioinformaticians, (bio)chemists and biologists. IRIBHM is located on the Erasme campus next to the academic hospital and the Jules Bordet Institute for cancer research and treatment. Researchers of the Institute have access to state-of-the-art genomics, proteomics, transgenesis, FACS and confocal microscopy technological platforms.

Beck's laboratory. The research conducted in the laboratory headed by Pr. Benjamin Beck at IRIBHM is focused on two main topics: (i) the characterization of the molecular processes involved in the development of esophageal metaplasia and adenocarcinoma and (ii) the identification of a molecular core in esophageal squamous cell carcinoma and its role in cancer growth and resistance to therapy. To address these questions, the laboratory uses a multidisciplinary approach relying on the use of transgenic mouse models, conditional knockout and overexpression systems, lineage tracing, 2D and 3D cell cultures from mouse and human esophageal cells, epigenetic and transcriptomic sequencing of FACS sorted cells including single cell RNA sequencing, 1D/2D-PAGE, kinase activity assays and mass spectrometry, Immunostaining, in situ hybridization and qPCR. Research is funded by FNRS, WELRI/WELBIO, the Worldwide cancer research, *Fondation Contre le Cancer*, Télévie and regional research programs.

Pr. Benjamin Beck obtained his PhD in Biomedical Science from the *Université des Sciences et Technologies de Lille* (France) in 2007. He thereafter pursued his research as postdoctoral fellow at the Stem Cell and Cancer Lab of ULB under the supervision of Pr. C. Blanpain between 2008 and 2015 and joined the IRIBHM thereafter as Research associate to launch his own research laboratory. In 2021, he became deputy director of the IRIBHM and was appointed as principal investigator of the Belgian National Fund for Scientific Research (FNRS). He is the author of 40 peer-reviewed articles published in high impact journals such as Nature, Nature Medicine, Science Advances, Cell Stem Cell, PNAS, EMBO Journal, Cancers, Cancer Research, FASEB.

RELEVANT PUBLICATIONS

> SHIP2-PLK1 crosstalk promotes sensitivity to dual inhibition in esophageal squamous cell carcinoma.
Molecular Cancer in press (2025). doi: https://doi.org/10.1186/s12943-025-02454-z



SHIP2 Inhibition In eSCC Cells Enhances Sensitivity To PLK1 Inhibitor

Percentage of eSCC cell survival measured after a 72-hour treatment with DMSO, K149, Volasertib or the combination of K149 (SHIP2 inhibitor) and Volasertib (PLK1 inhibitor) in cell lines KYSE-520 and COLO-680.

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