Targeting Long-Chain Fatty Acid Elongation Disrupts Cancer Membranes Organization and Triggers Anti-Cancer Immunity

ISREC Institut Suisse de Recherche Expérimentale sur le Cancer @EPFL

Experimental Hematology / Oncology

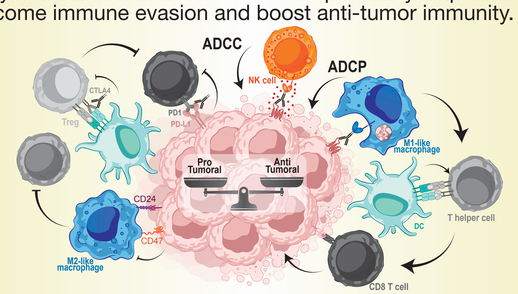
Justine Epiney[1,2,3], Albert Santamaria-Martínez[1,2], Asli Kasapoglu[1,2], Gabor Dienes[1,2], Natalya Katanayeva[1,2], Pierre Miranda[4], Laurence Abrami[5], Jean Maillat[5], Linda Wedemann[5], Maria Pavlou[6], Romain Hamelin[6], Florence Armand[6], Janna Hasting[7,8], Pierre Fournier[9], Frederic Bretagnol[9] Milena Schuhmacher[5], Gisou van der Goot[5], Thommas Hannich[10], Giovanni D'Angelo[5] & Elisa Oricchio[1,2]

SOHC SWISS ONCOLOGY & HEMATOLOGY CONGRESS

[1]Swiss Institute for Experimental Cancer Research, EPFL, Lausanne; [2]Swiss Cancer Center Léman, Switzerland; [3]Hemato-oncology department, CHUV, Lausanne; [4]Institute of Chemical Sciences and Engineering, EPFL, Lausanne; [5]Institute of Bioengineering and Global Health Institute, EPFL, Lausanne; [6]The Proteomics Core Facility, EPFL, [7]Lausanne; School of Medicine, University of St Gallen, St Gallen, [8]Institute for Implementation Science in Health Care, University of Zurich, Zurich; [9]Service de chirurgie, GHOL, Nyon; [10]CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences, Lazarettgasse 14, 1090, Vienna, Austria.

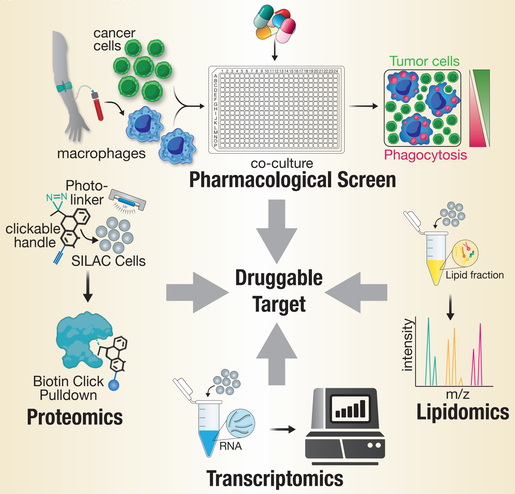
INTRODUCTION

Cancer cells evade immune cell recognition by hijacking spatially organized receptor-ligand interactions. To discover critical dependencies of immune evasion, we performed a large-scale small-molecule co-culture screening paired with proteomics, and lipidomics. Targeting long-chain fatty acid (LCFA) elongation altered the membrane organization of cancer cells, but not immune cells. Pharmacological and genetic inhibition of HSD17B12, a key enzyme in LCFA elongation, reduced very-long-chain fatty acid (VLCFA) synthesis, selectively affecting cancer cells by altering membrane organization and receptor distribution, including immune checkpoints and lipid transporters. In contrast, HSD17B12 inhibition enhanced glycolytic and cytotoxic activity of macrophages, T, and NK cells. Through these divergent phenotypes, targeting HSD17B12 reduced tumor growth and promoted immune activation in preclinical models. This study reveals a cancer-specific dependency on VLCFAs that can be therapeutically exploited to overcome immune evasion and boost anti-tumor immunity.



AIMS & METHODS

By combining high-throughput pharmaceutical screening with transcriptomics, proteomics, and lipidomics, we aimed at identifying novel druggable targets enhancing anti-cancer immunity.



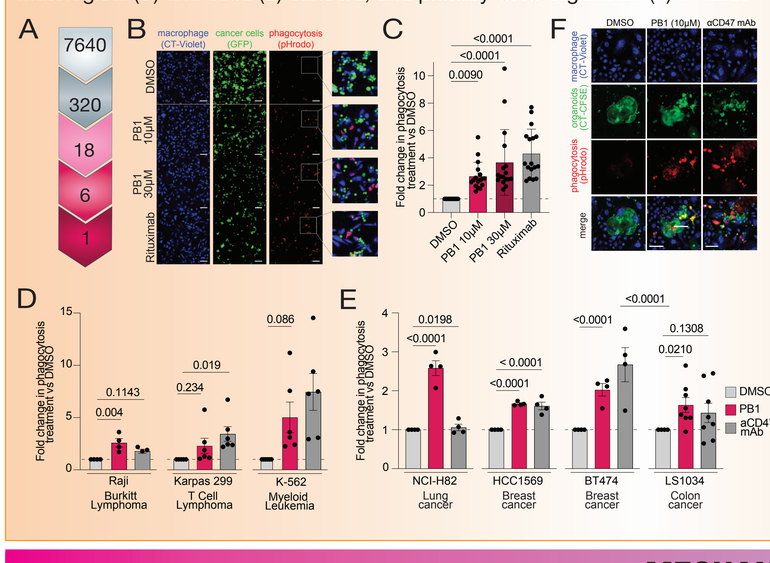
Conclusion

In summary, our findings reveal HSD17B12 as a cancer-specific metabolic vulnerability that controls membrane organization and immune evasion. Targeting this pathway selectively impairs tumor cells while enhancing immune function, offering a novel strategy to restore anti-tumor immunity. Future work will focus on medicinal chemistry optimization and preclinical studies to advance HSD17B12 inhibitors toward clinical translation.

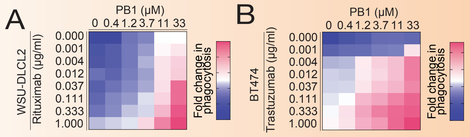
Presented at SOHC 2025 from 19 - 21 November 2025

IDENTIFICATION OF A PRECLINICAL COMMPOUND : PB1

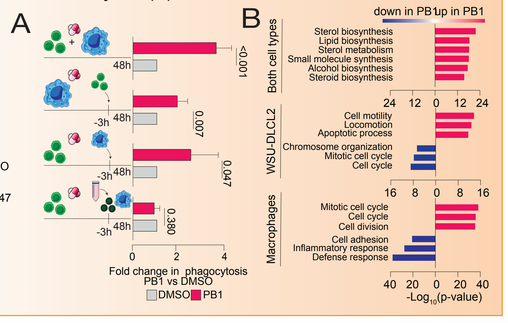
1. A pharmacological screen identifies a new compound, PB1, that enhances phagocytosis. Out of 7,640 molecules (A), PB1 significantly increases the phagocytosis of lymphoma cells (B-C), as well as other models of hematological (D) and solid (E) cancers, and primary CRC organoids (F) in vitro.



2. PB1 synergizes with monoclonal antibodies, including Rituximab in lymphoma (A) and Trastuzumab in breast tumors (B).

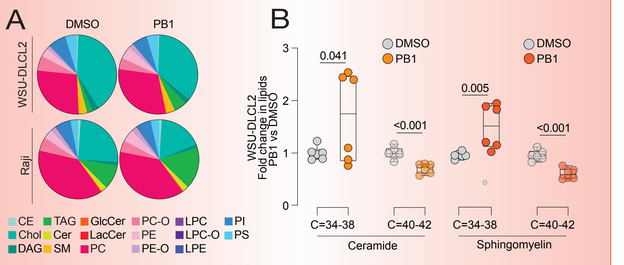


3. PB1 affects both cancer cells and macrophages (A). It upregulates lipid metabolism in both cell types but leads to opposite effects on the cell cycle (B).

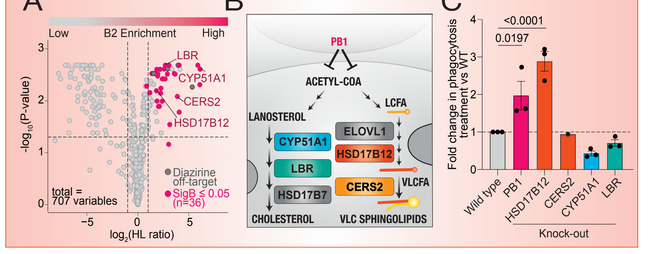


PB1 MOLECULAR TARGET

4. Lipidomics analysis shows that PB1 leads to a decrease in very long-chain sphingolipids and cholesterol (A and B).

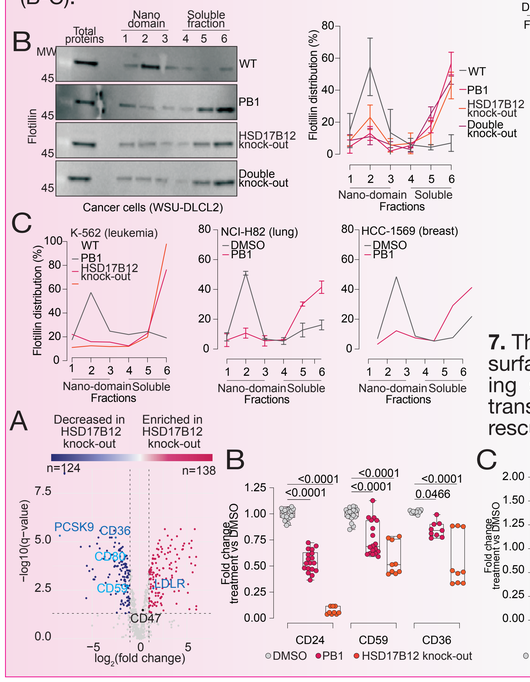


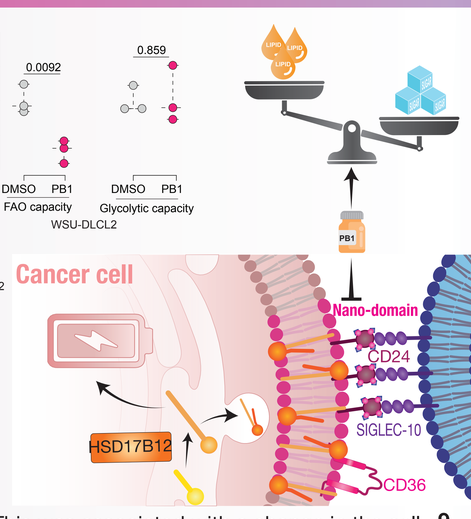
5. Proteomics analysis (A) identifies HSD17B12, involved in long-chain fatty acid elongation (B), as a target of PB1 (C).



MECHANISM OF ACTION

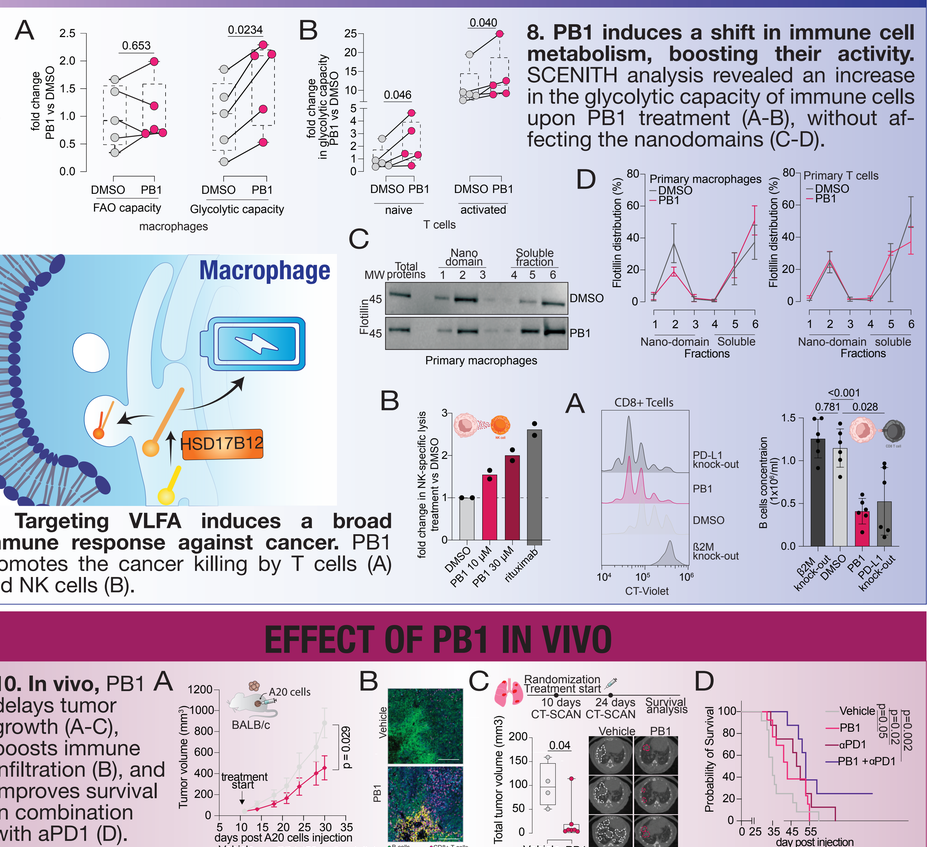
6. Genetic or pharmacological inhibition of long-chain fatty acid elongation exerts specific effects in cancer cells. Using SCENITH, we found a decrease in fatty acid oxidation in cancer cells (A). Additionally, DRM assays indicate that PB1 disrupts lipid nanodomains in various cancer cell lines (B-C).





7. This was associated with a change in the cell surface repertoire of knock-out cells (A), including several "don't eat me" signals and lipid transporters (B), which were restored upon rescue of the nanodomains (C-D).

8. PB1 induces a shift in immune cell metabolism, boosting their activity. SCENITH analysis revealed an increase in the glycolytic capacity of immune cells upon PB1 treatment (A-B), without affecting the nanodomains (C-D).



9. Targeting VLFA induces a broad immune response against cancer. PB1 promotes the cancer killing by T cells (A) and NK cells (B).

EFFECT OF PB1 IN VIVO

10. In vivo, PB1 delays tumor growth (A-C), boosts immune infiltration (B), and improves survival in combination with aPD1 (D).