

Andrada Constantinescu <sup>1</sup>, Raquel Pequeru <sup>1,2</sup>, Bassam Janji <sup>3</sup>, Akinchan Kumar <sup>3</sup>, Jaime Farrés <sup>2</sup>, Mileidys Pérez-Alea <sup>1</sup>, Rocío Rebolledo-Ríos <sup>4</sup>

<sup>1</sup> Advanced BioDesign, Parc Technologique de Lyon, Saint Priest, France / <sup>2</sup> Department of Biochemistry and Molecular Biology, Faculty of Biosciences, Universitat Autònoma de Barcelona, Bellaterra, Spain /

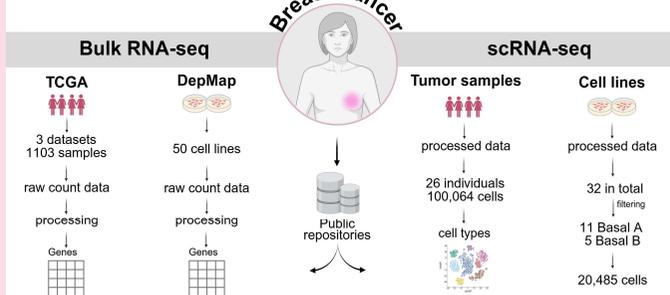
<sup>3</sup> Tumor Immunotherapy and Microenvironment Research Group, Luxembourg Institute of Health, Luxembourg / <sup>4</sup> Faculty of Medicine and University Hospital of Cologne, Department I of Internal Medicine, University of Cologne, Cologne, Germany

## Introduction

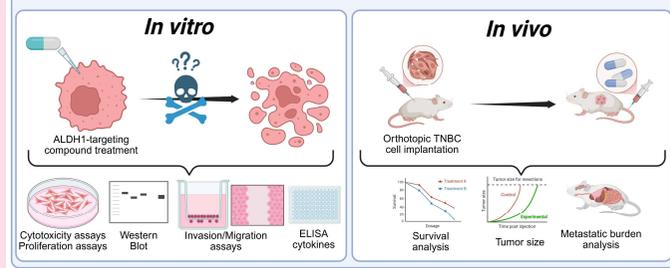
Triple-negative breast cancer (TNBC) is among the most aggressive and clinically challenging breast cancer subtypes, marked by high metastatic potential, poor prognosis and limited treatment options. This underscores the urgent need to identify novel molecular targets for effective therapies. Aldehyde dehydrogenase 1 (ALDH1) enzymatic activity is a hallmark of cancer stem cells (CSCs), strongly associated with drug resistance, tumor aggressiveness, and metastasis, making it an attractive therapeutic target. However, the distinct roles of ALDH1 isoforms remain poorly understood, hindering the rational design and clinical application of selective ALDH1 inhibitors.

## Material and methods

### Transcriptomic analyses



### Functional studies

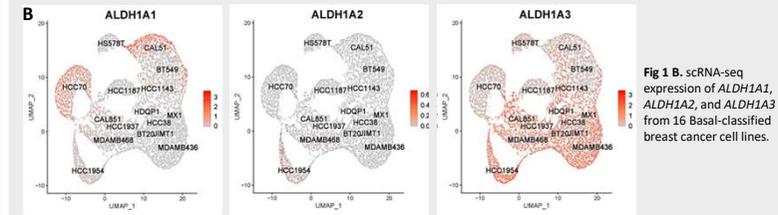
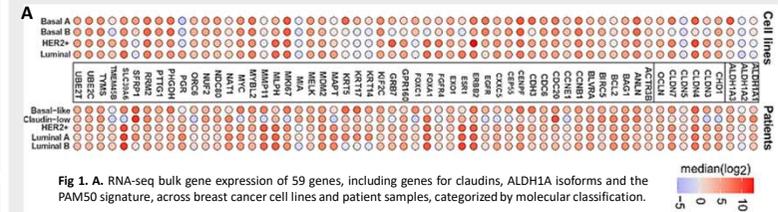


## Conclusions

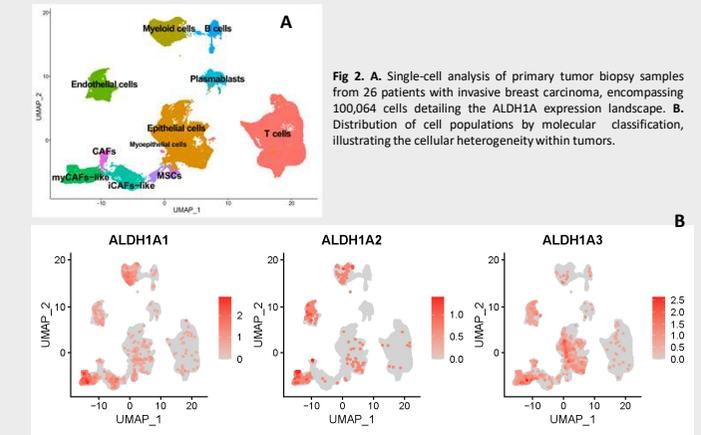
- **ALDH1A3 is significantly overexpressed in basal-like TNBC and in claudin-low breast cancer cells.**
- **ABD0171 exhibits potent anticancer and antimetastatic activity, inducing the extrinsic apoptotic pathway and abrogating the activation of STAT3.**
- **ABD0171 shows tumor growth-inhibitory activity in both xenograft and syngeneic TNBC tumor models.**

## Transcriptomic results

- ALDH1A3 and 1A1 are highly expressed in breast cancer, with ALDH1A3 expression significantly higher in basal-like molecular subtypes.**

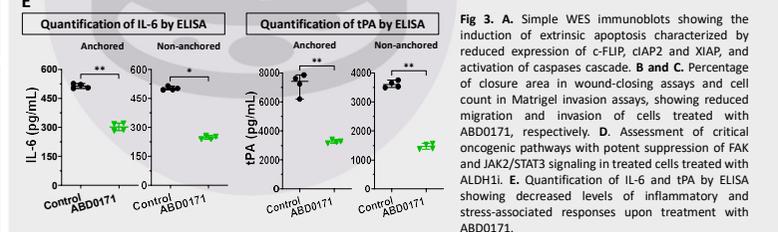
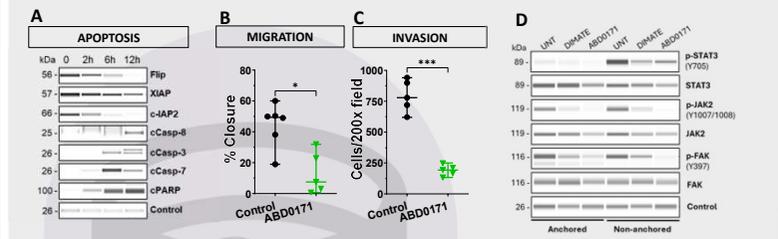


- ALDH1A3 and 1A1 are expressed in Myofibroblast-like cancer-associated fibroblasts (myCAFs) and ALDH1A3 is also highly expressed in epithelial cells.**

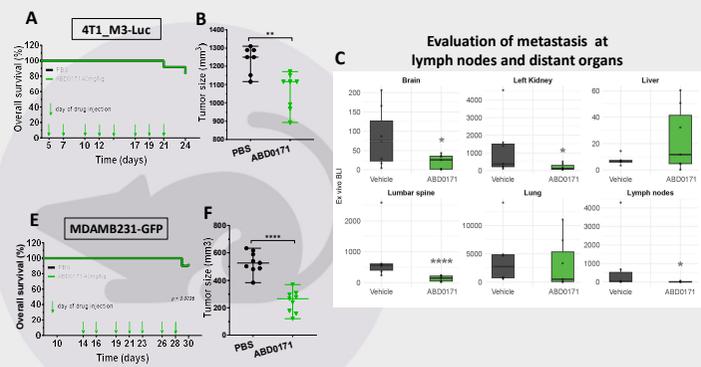


## Functional studies

- The novel ALDH1 inhibitor - ABD0171, induces extrinsic apoptosis and inhibits migration and invasion by suppressing STAT3 activation.**



- ALDH1 ABD0171 inhibits tumor growth and has antimetastatic activity in TNBC preclinical models.**



**Fig 4. A and E.** Kaplan-Meier survival curves of two different TNBC animal models, treated with ABD0171. **B and F.** Inhibition of primary tumor growth with ABD0171. **C.** Evaluation of metastasis in 4T1\_M3 model treated with ABD0171; the metastatic burden is significantly reduced in the lymph nodes, brain, lumbar spine and kidney.

## References

Pommier et al., *Nat Commun.* 2020 Jul 9;11(1):3431.  
Gambardella et al., *Nat Commun.* 2022 Mar 31;13(1):1714  
Wu et al., *Nat Genet.* 2021 Sep;53(9):1334-1347.  
Qin et al., *J Exp Clin Cancer Res.* 2019 May 14;38(1):195.  
Ortiz et al., *Cell Commun Signal.* 2021 Jun 30;19(1):67.  
Bharadwaj et al., *Mol Oncol.* 2024 Jan;18(1):91-112.