

Dissecting the roles of lipid uptake in kidney tumors

Javier Garcia-Bermudez, Assistant Professor

Children's Research Institute at UT Southwestern

September 11-13, 2025



KidneyCancerAssociation® IN PARTNERSHIP WITH

UTSouthwestern
Medical Center
Kidney Cancer Program

Tumors activate de novo lipid synthesis, but simultaneously intensify the uptake of lipids from the diet

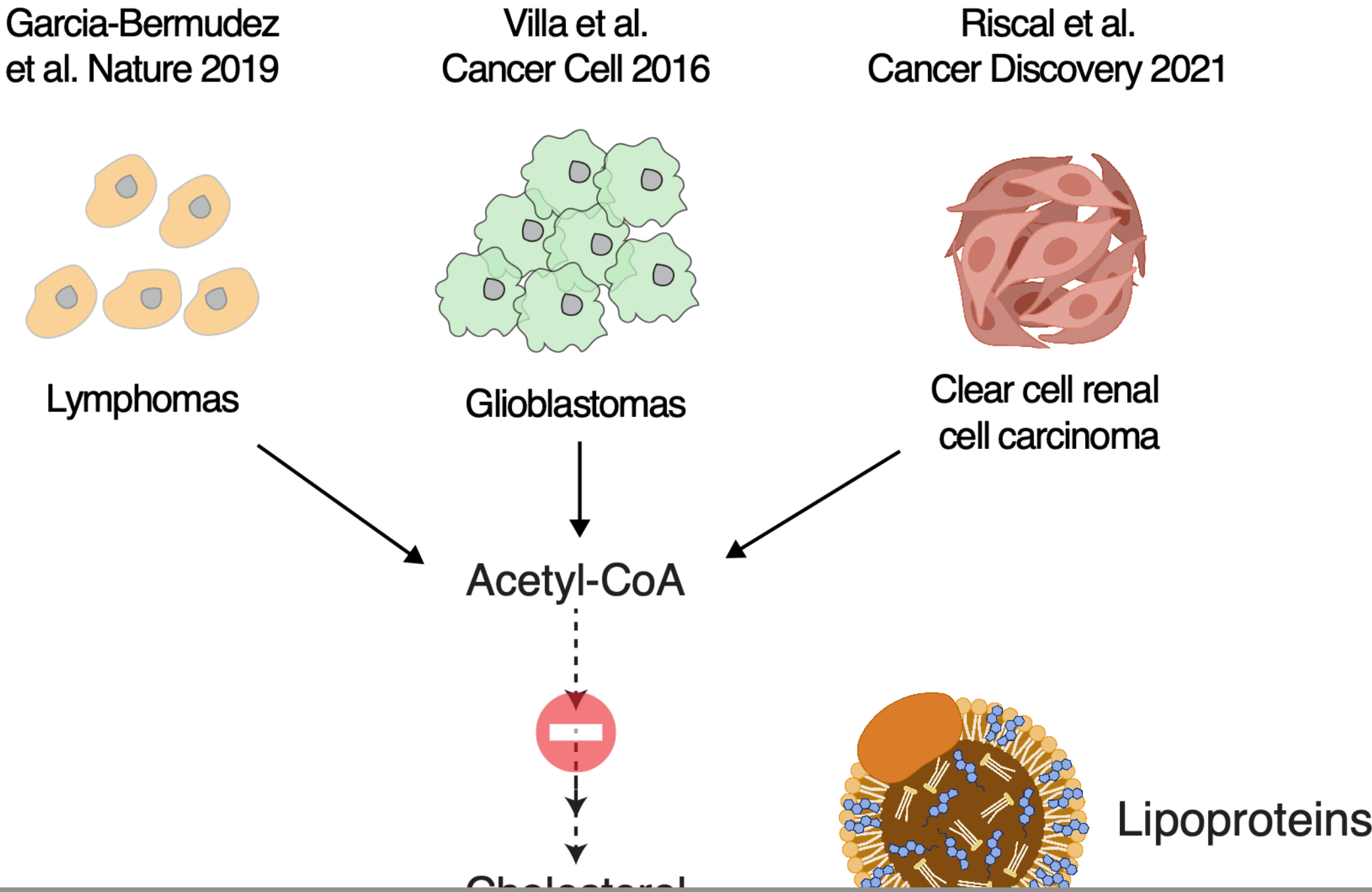
First of many studies showing increased lipid synthesis in cancer compared to normal tissues (1950s).

Metabolism of Neoplastic Tissue. IV. A Study of Lipid Synthesis in Neoplastic Tissue Slices *in Vitro**

GRACE MEDES, ALICE THOMAS, AND SIDNEY WEINHOUSE

(Lankenau Hospital Research Institute and the Institute for Cancer Research, Philadelphia. Pa.)

Studies showing constitutively high lipoprotein uptake in cholesterol-auxotroph cancers.

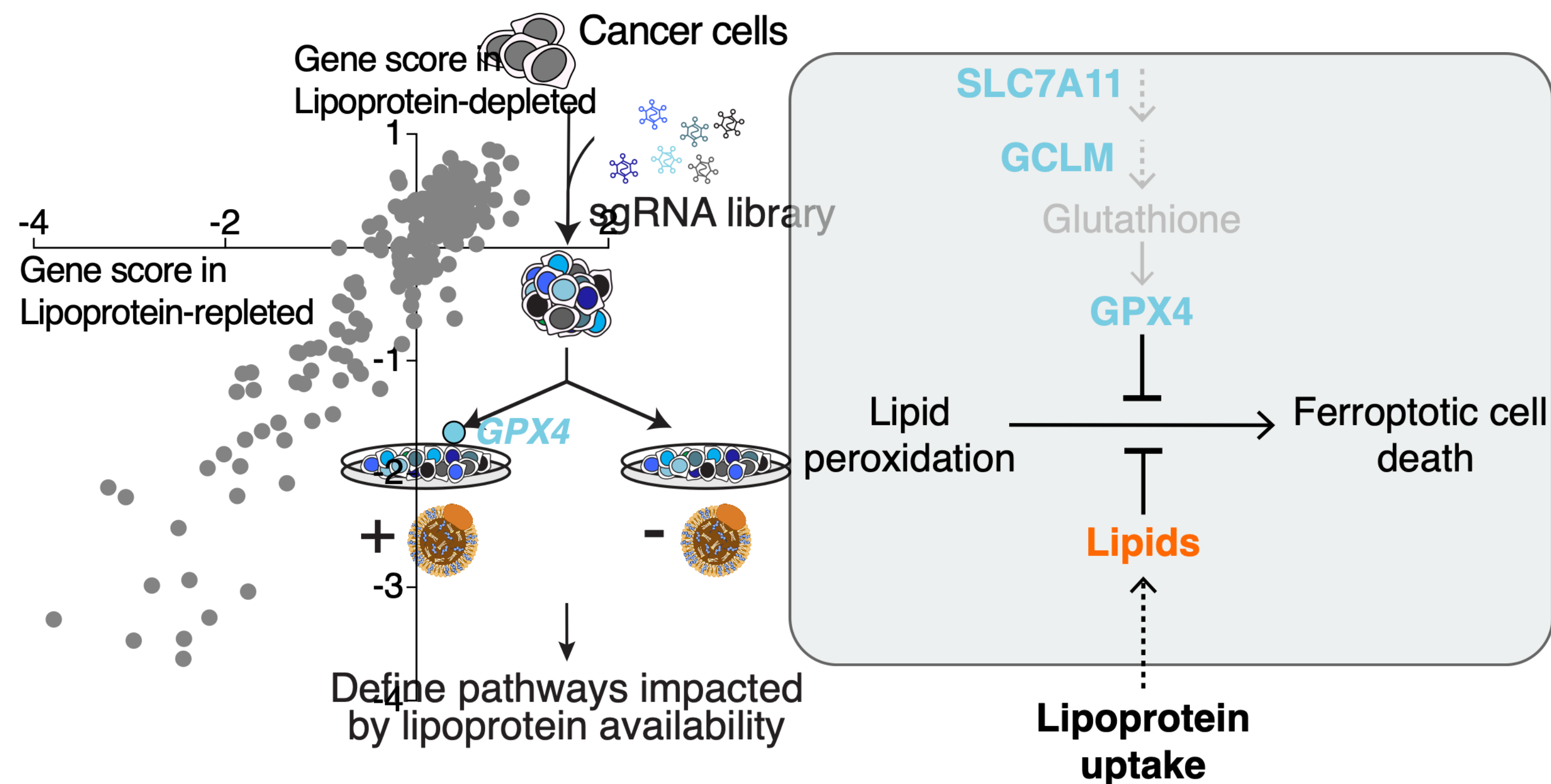


Hypothesis: Exogenous lipid pools provide tumors with functional advantages that synthesis cannot fulfill

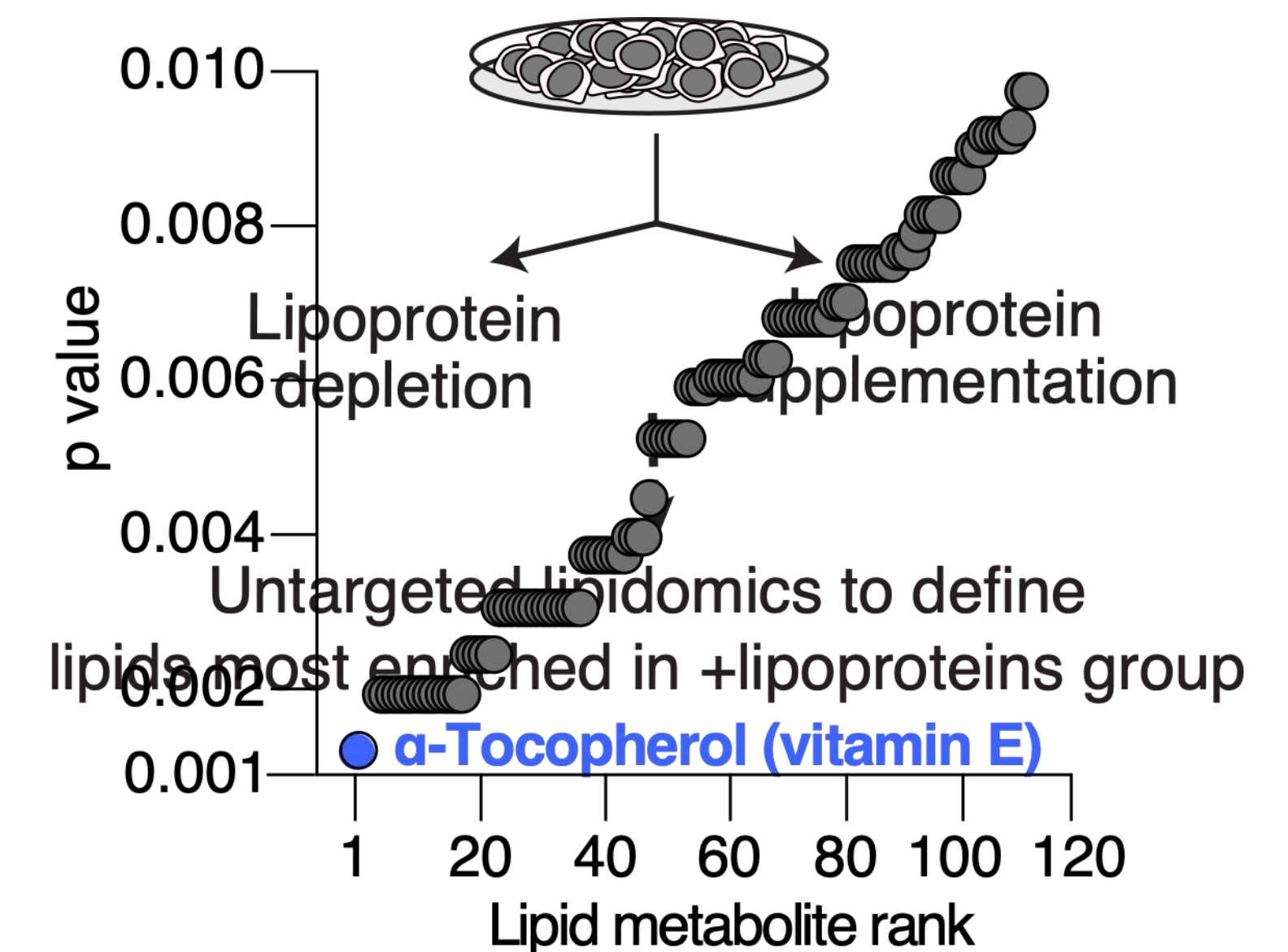
that in most cancer cell lines we have tested.

Lipoproteins transport hundreds of lipids, requiring unbiased approaches for functional analysis

Approach 1: CRISPR screen in cancer cells
+/- purified human lipoproteins (LDL and HDL)

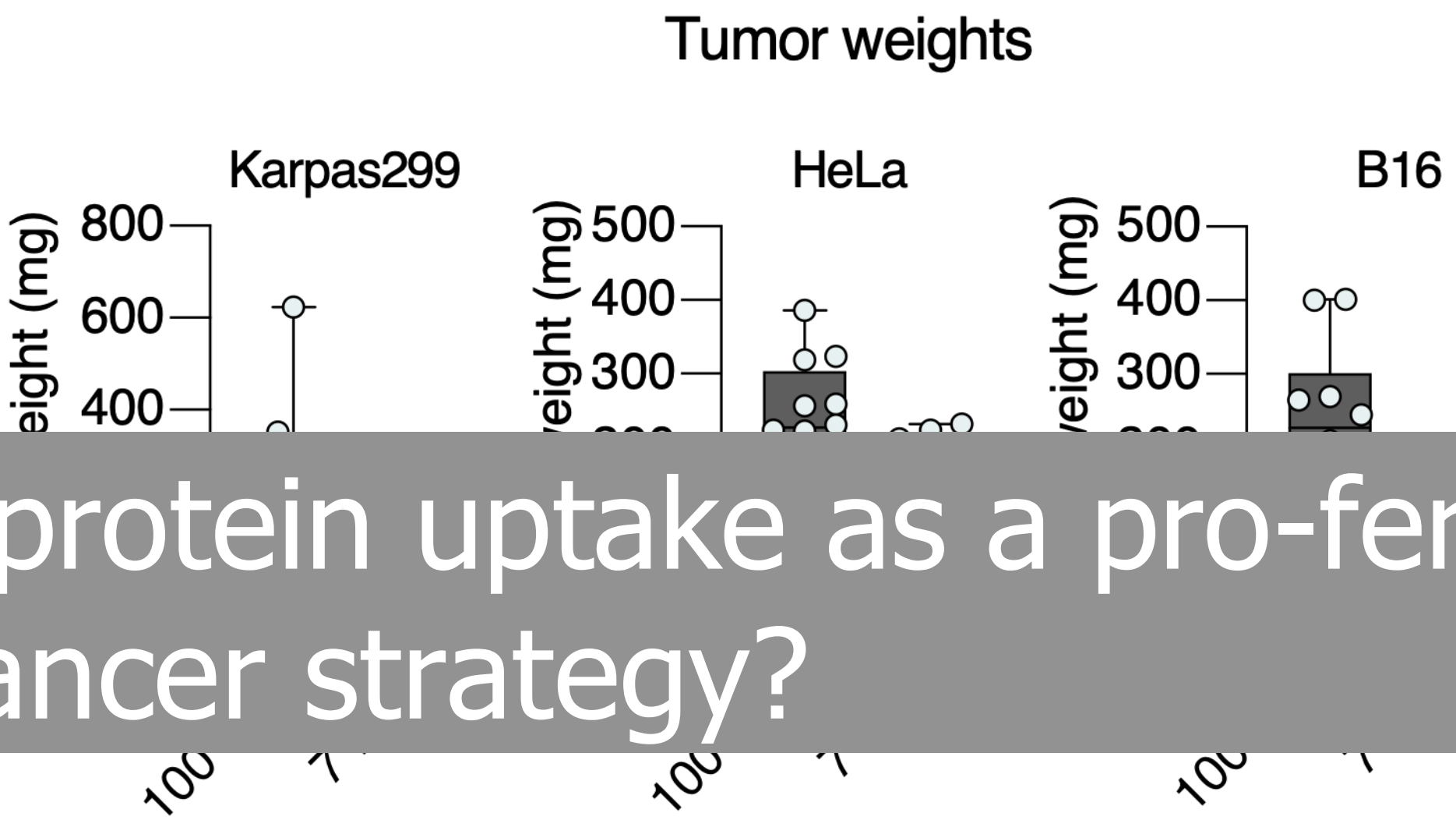
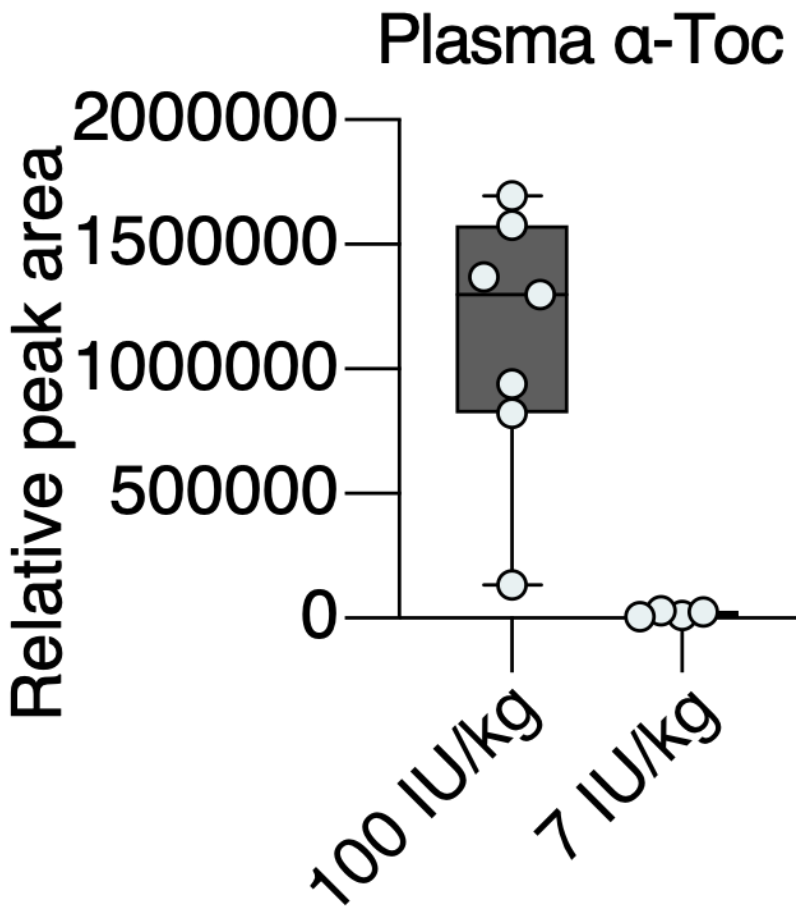
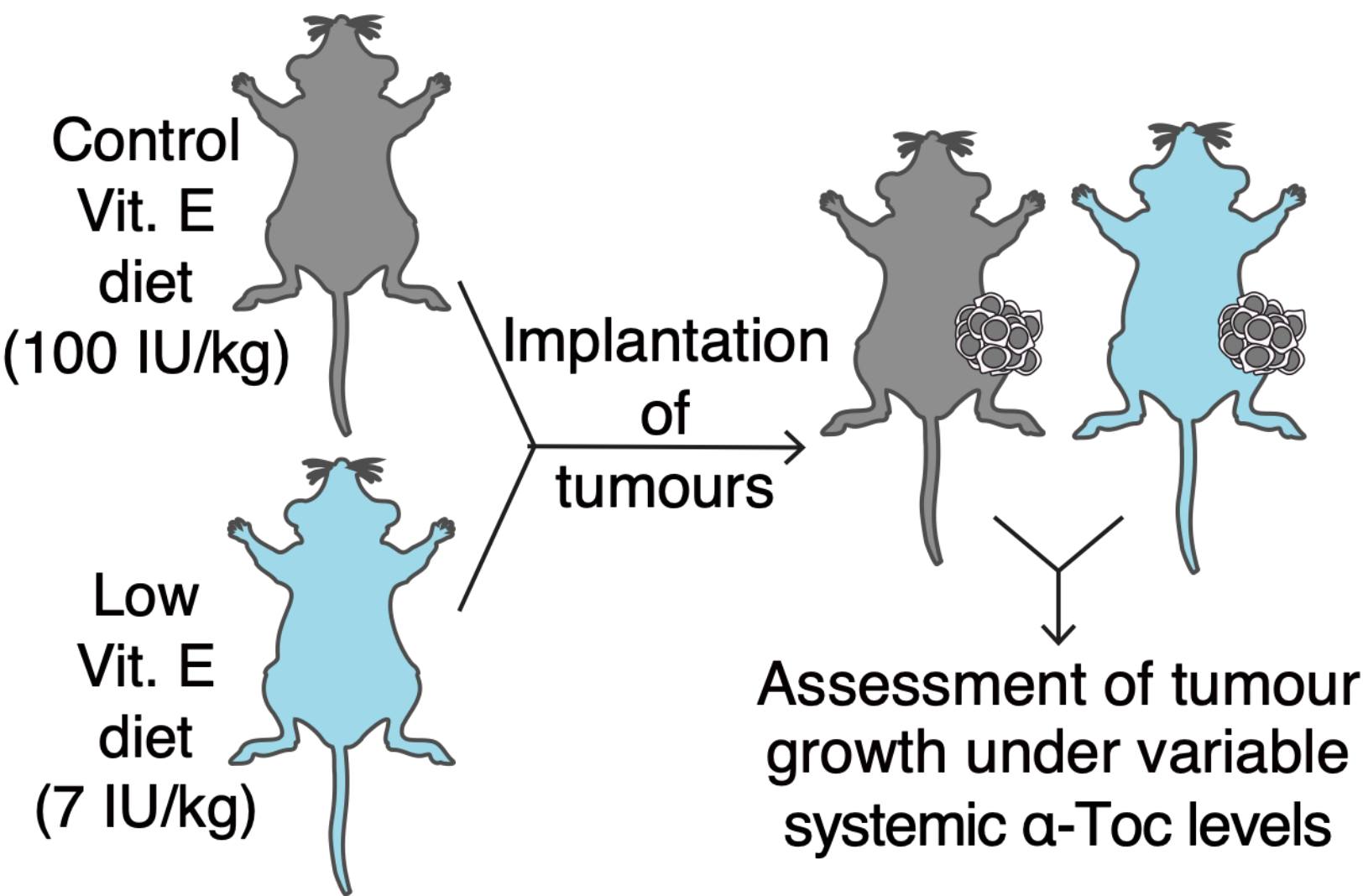
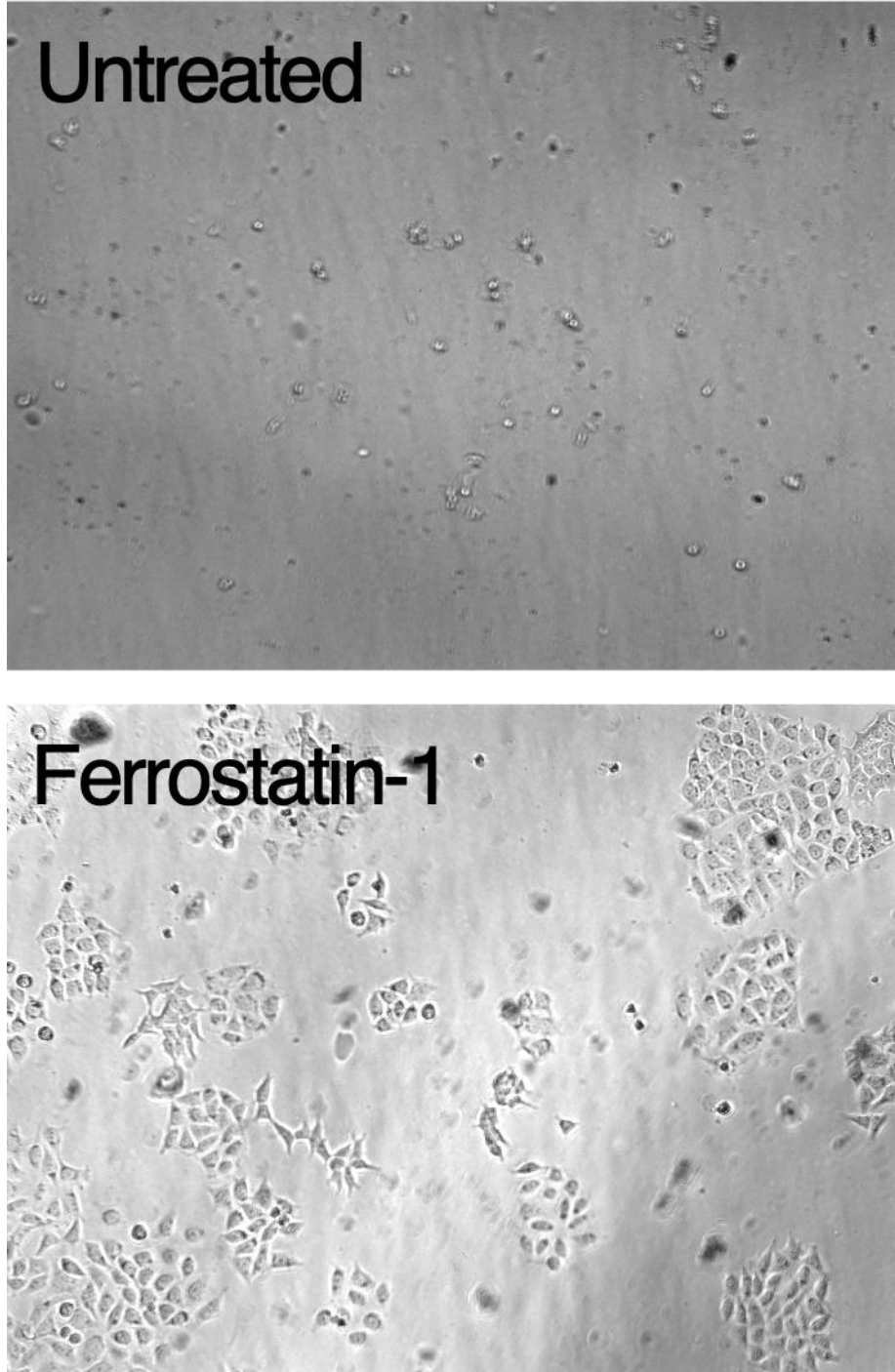
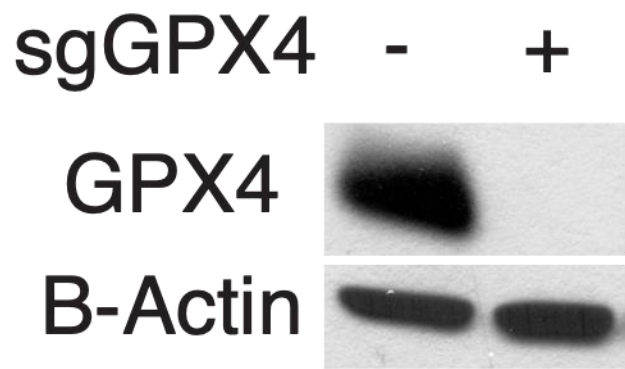


Approach 2: Untargeted lipidomics in
cancer +/- lipoproteins



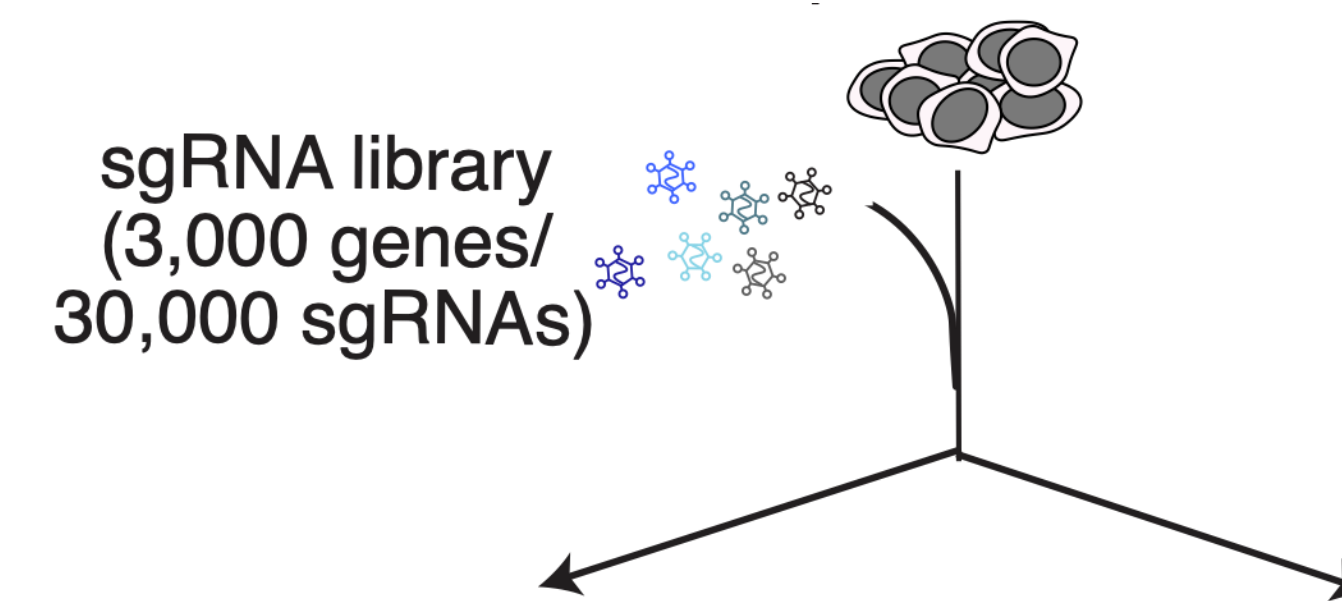
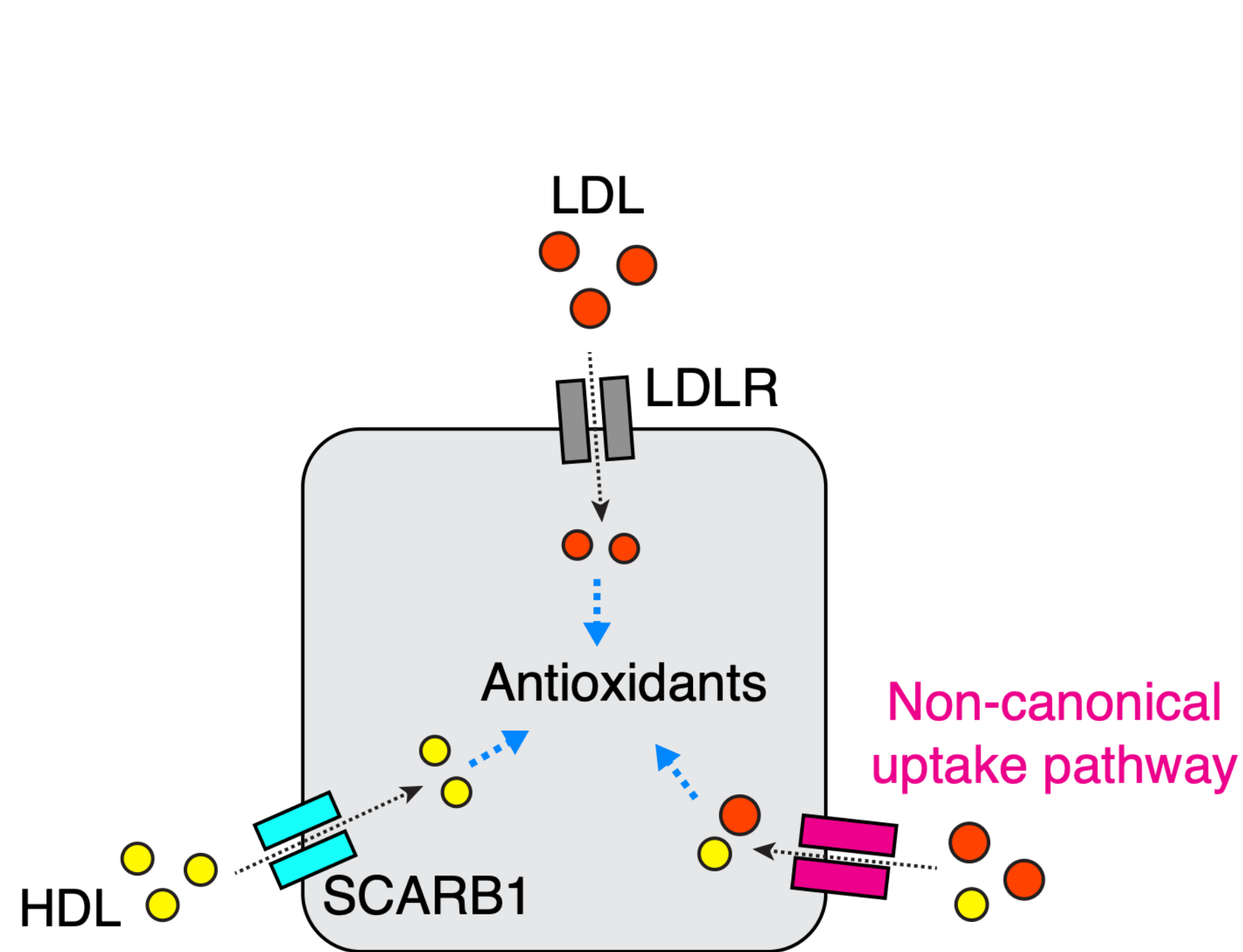
Lipoprotein-delivery of α -tocopherol drives ferroptosis resistance and tumor growth in mice

A-498 GPX4_KO (ccRCC)

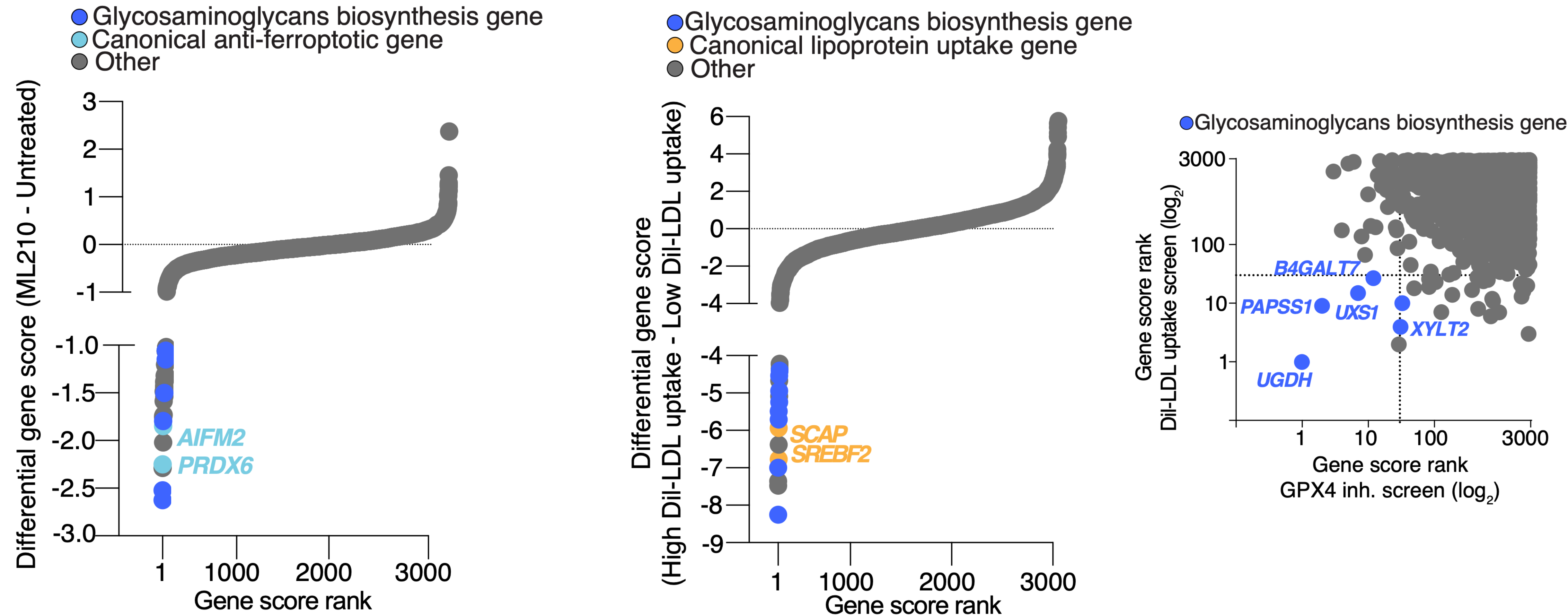


Can we inhibit cancer lipoprotein uptake as a pro-ferroptotic anti-cancer strategy?

Orthogonal CRISPR screens to discover cancer lipoprotein uptake mechanisms

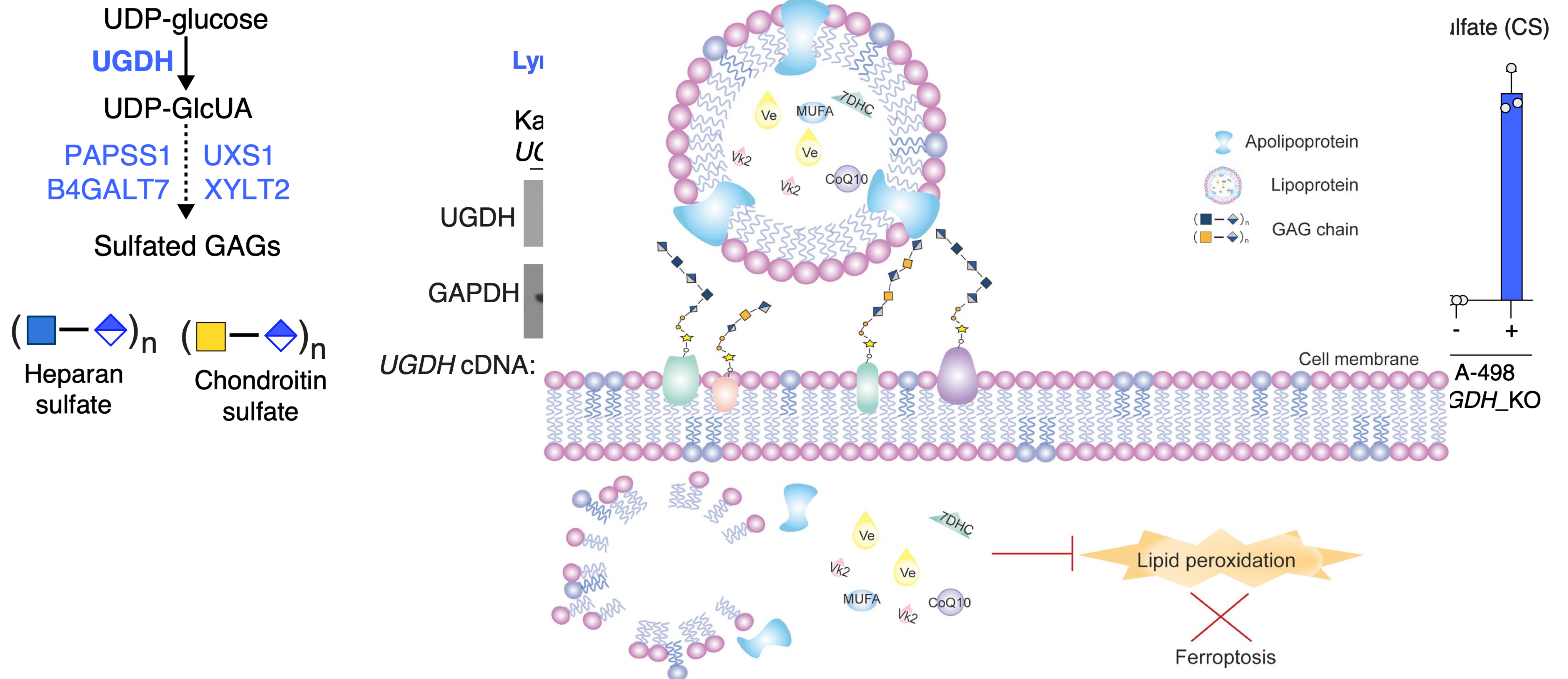


Cancer cells rely on a glycosaminoglycan-dependent pathway to take up lipoproteins

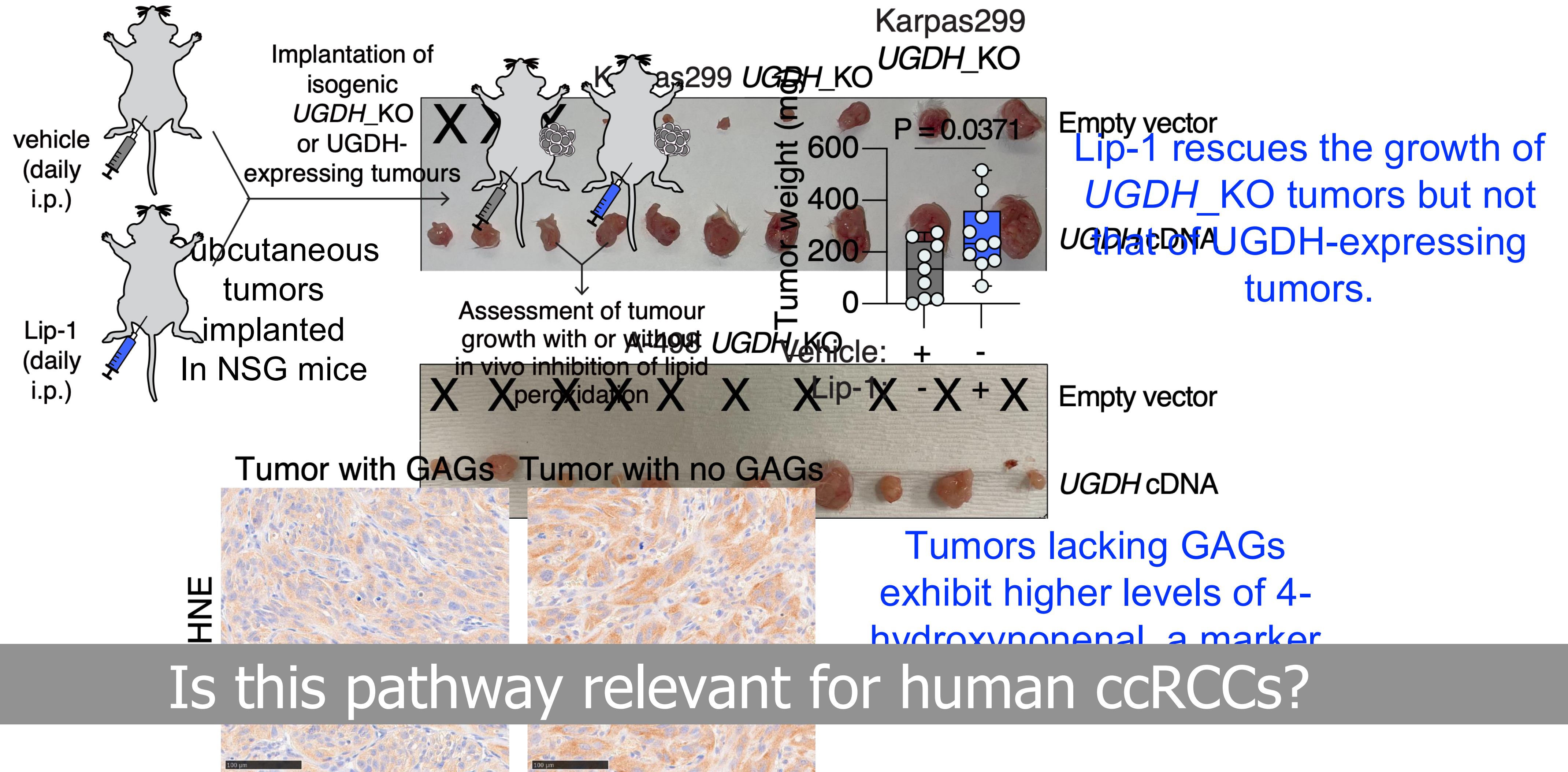


Tumor GAGs are the major pathway promoting LDL and HDL uptake in cancer cells

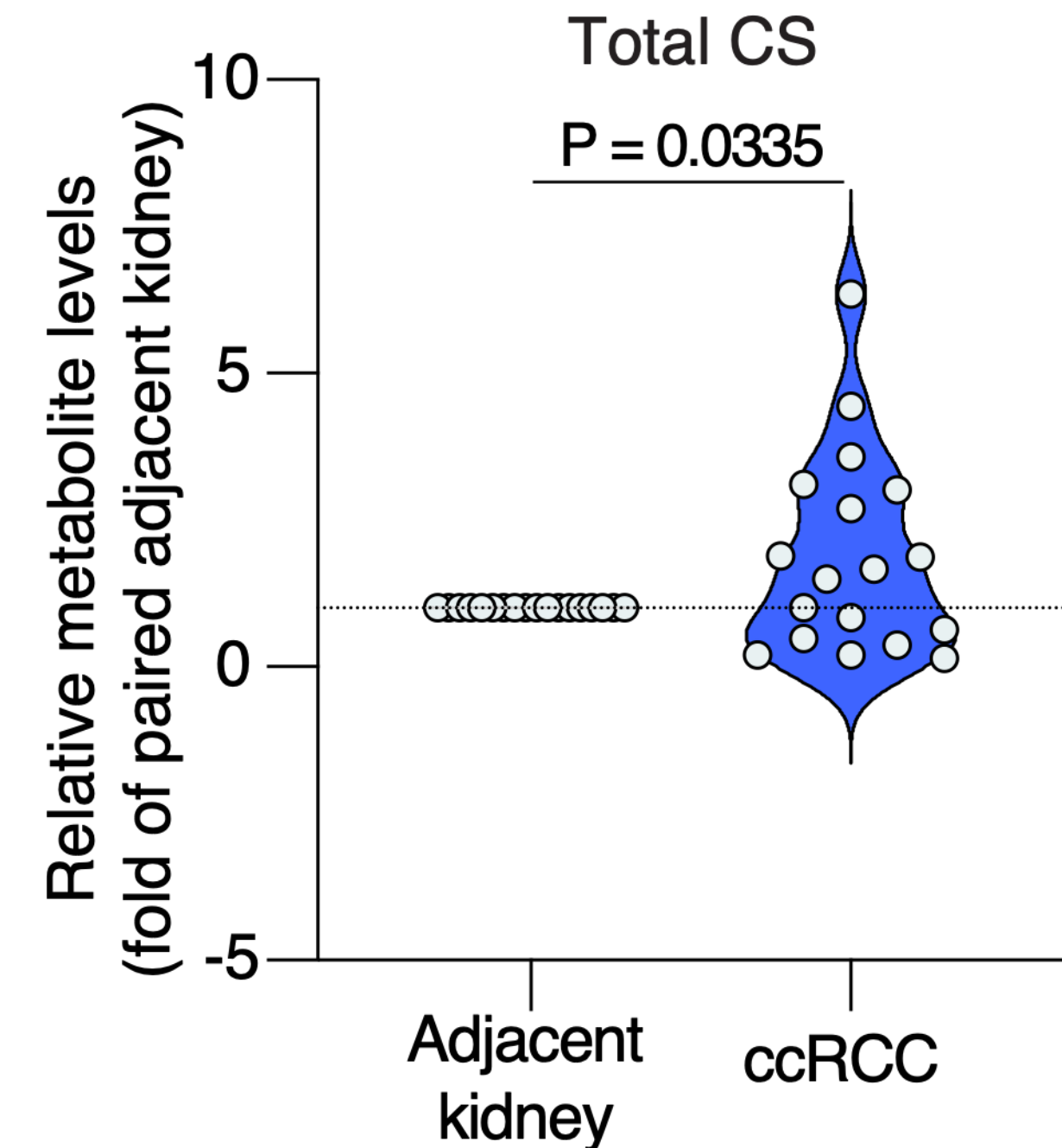
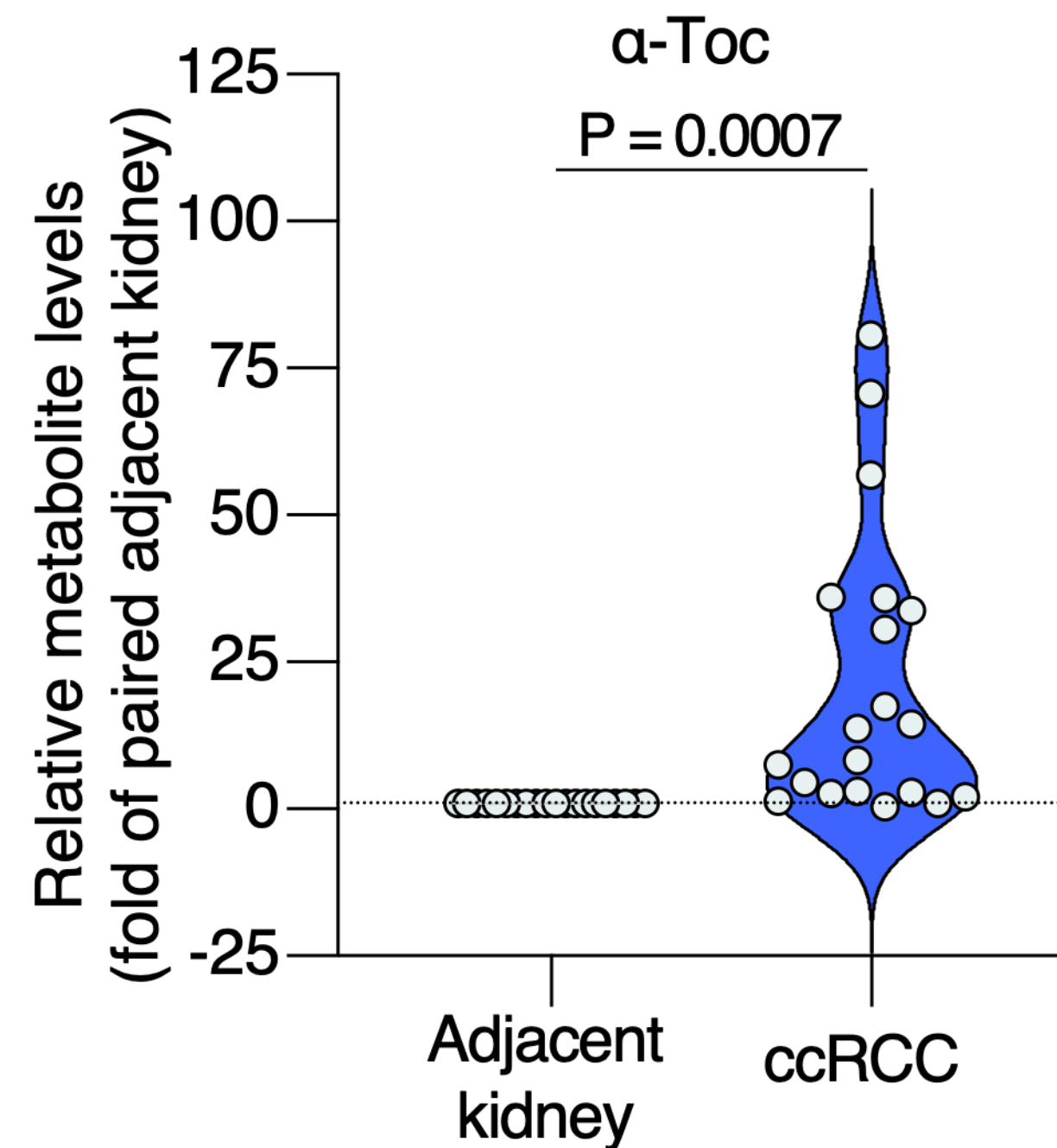
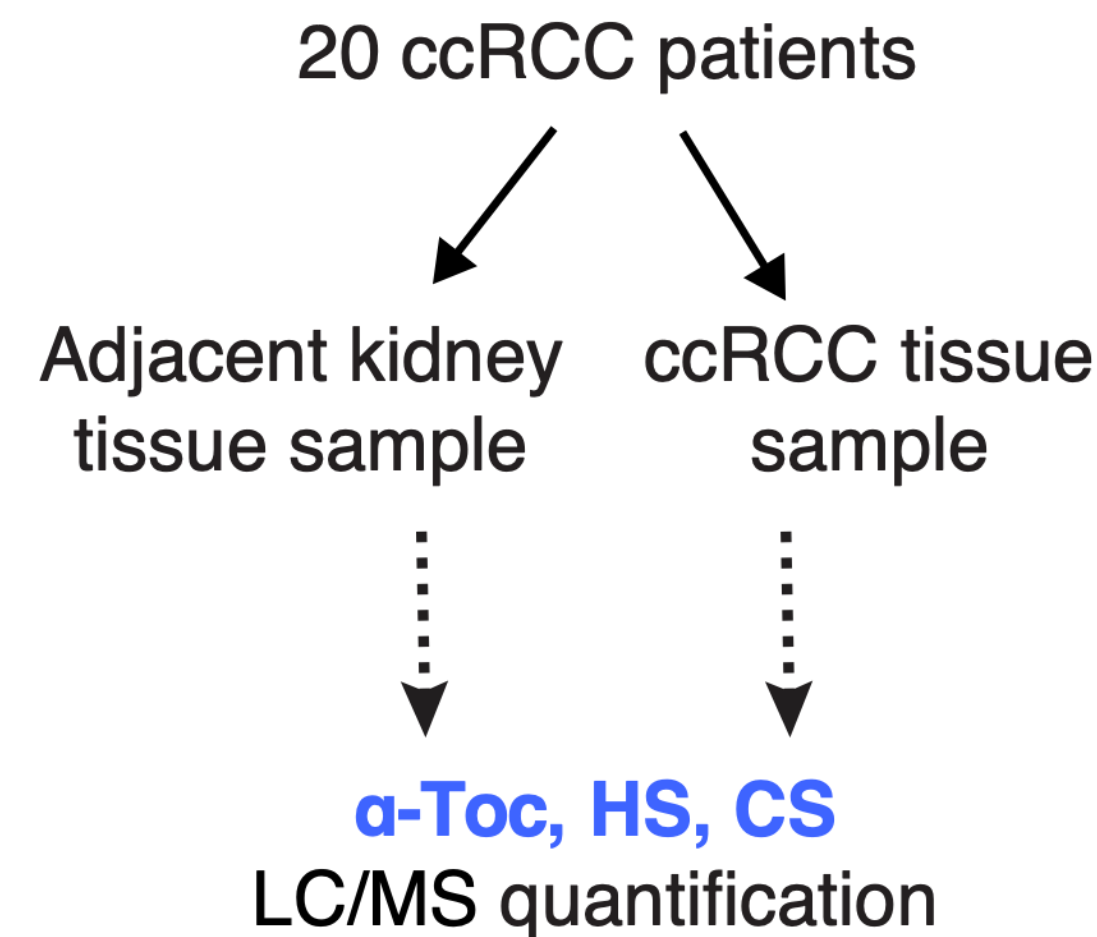
Calhoun, et al. Nature (2025)



The anti-ferroptotic effect of tumor GAGs is essential for tumor growth

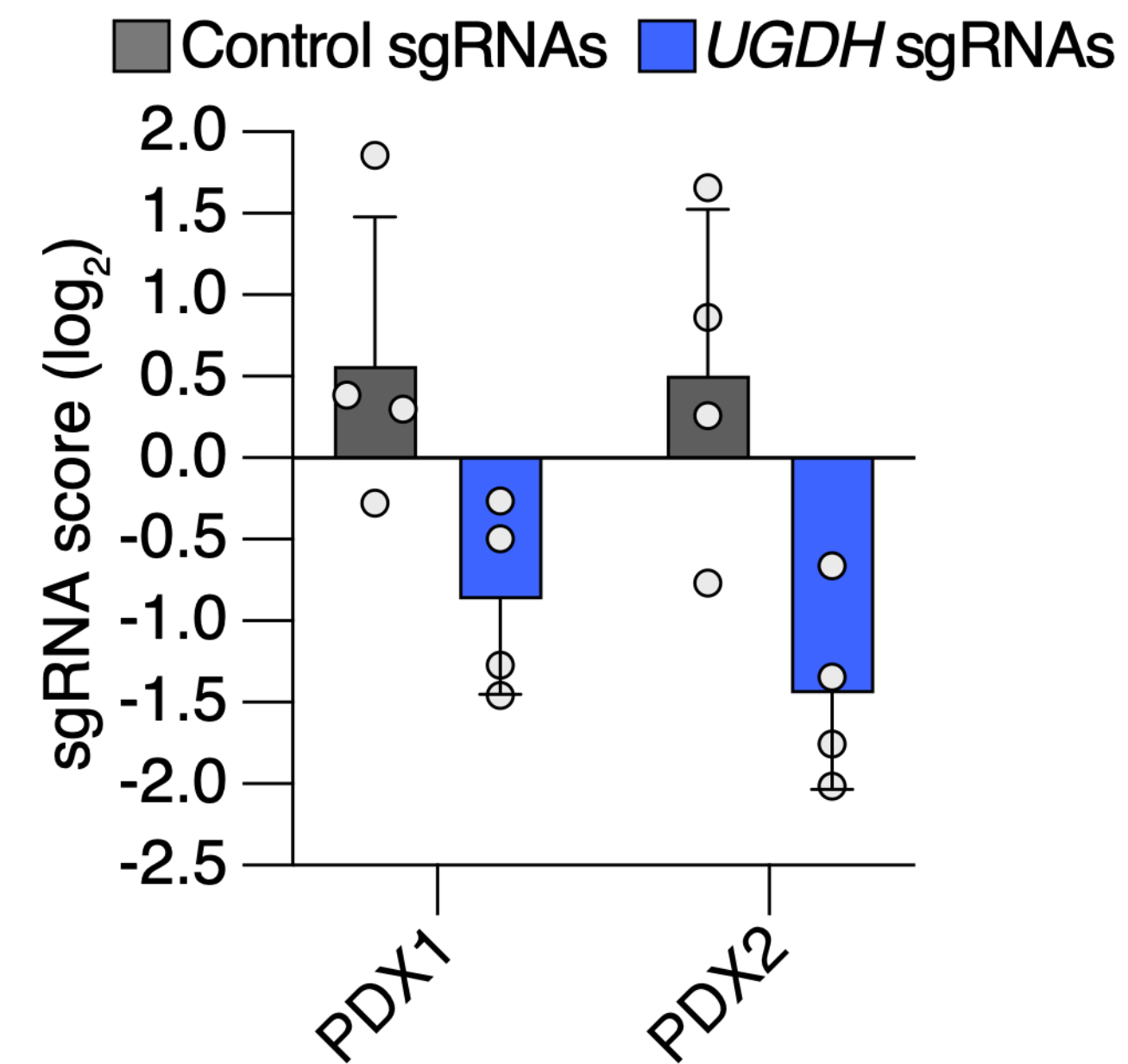
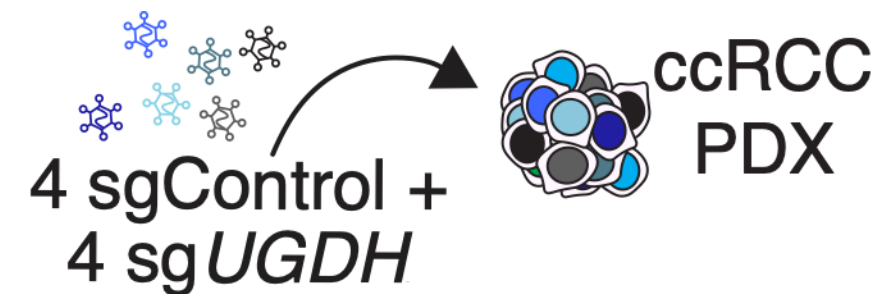


ccRCC patient samples exhibit higher levels of α -tocopherol and GAGs compared to matched adjacent kidney tissue



*with Dr. Margulis/DeBerardinis lab (UTSW)
and Weiss lab (UGA)*

GAG biosynthesis is essential for the orthotopic growth of ccRCC patient-derived xenografts (PDXs)



*with James Brugarolas lab
(Vanina Toffessi-Tcheuyap)*

Takeaway 1: Lipoproteins are readily available antioxidant reservoirs for tumors growing in mice and humans (~10x more than in cell culture).

Takeaway 2: We identify cell-surface GAGs as the key contributor to lipoprotein uptake, and the depletion of tumor GAGs as a strategy to induce tumor ferroptosis.

Example of the power of integrating cell line-based and primary models: Combination of (i) large-scale, high-throughput, unbiased approaches (CRISPR screens and untargeted lipidomics) in established cancer cell lines with (ii) targeted candidate analyses in pre-clinical models (targeted lipidomic analysis in human samples and single-gene KO in PDXs)

Acknowledgements

Kivanc Birsoy (Rockefeller University)

Vitaly Margulis M.D. (UTSW)

Garcia-Bermudez Lab

Dylan Calhoon

Lingjie Sang

Miaomiao Yu

Sheng-Chieh Hsu

Fubo Ji

Yong Wang

Renfei Wu

Nathaniel Kim

Yinuo Liu

DeBerardinis Lab (UTSW)

Feng Cai

Ling Cai

Pratt Lab (U Ottawa)

Weiss Lab (UGA)

Amrita Basu

Brugarolas Lab (UTSW)

Vanina Toffessi-Tcheuyap

Siuzdak lab (Scripps)



α -tocopherol is significantly enriched in human lipoproteins

