2nd International Electronic Conference on Metabolomics
20-27 November 2017
chaired by Dr. Peter Meikle
sponsored by metabolites

Mapping Metabolic Networks in 3D spheroids using Stable Isotope-Resolved Metabolomics (SIRM)

Teresa W.-M. Fan[1,*], Salim S. El-Amouri [1], Jessica K. A. Macedo [1], and Andrew N. Lane [1]

[1] Center for Environ. & Systems Biochemistry; Markey Cancer Center; Dept. of Toxicology & Cancer Biology

*** Corresponding author: twmfan@gmail.com**

UK HealthCare Markey Cancer Center

NCI·CC A Cancer Center Designated by the National Cancer Institute

CESB Center for Environ... and Systems Biochem...

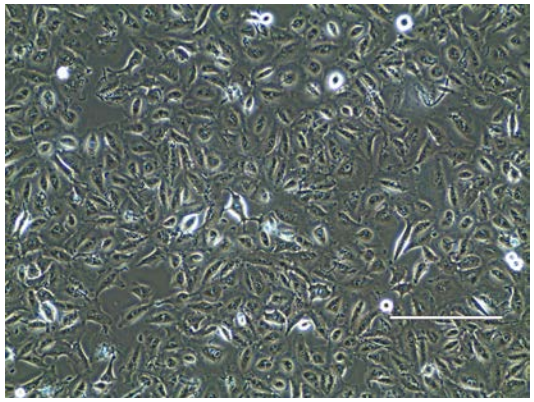
Introduction

- 2D cell cultures have unrealistic concentration gradients of O_2, nutrients, and treatment agents.
- 2D cell cultures lack cell-cell and cell-extracellular cellular matrix interactions (ECM).
- 3D cell cultures (spheroids in matrigel, hydrogels, micropattern plates, hanging drops, and M3DB systems) can overcome these drawbacks.
- Long speroid formation time, variable efficiency, handling complextiy, matrix contamination, and/or scaling-up are of concern for all but the M3DB systems.
- The M3DB (Magnetic 3D Bioprinting) method enables spheroid formation by magentizing cells with magnetic nanoparticles, which is easy to handle and can be scaled up readily for metabolomic studies.
- 3D spheroids display higher drug resistance than 2D cell cultures but the underlying metabolic mechanism is unclear.
- Stable Isotope-Resolved Metabolomics (SIRM) is well-suited for exploring drug-induced metabolic perturbations in M3DB spheroid cultures.

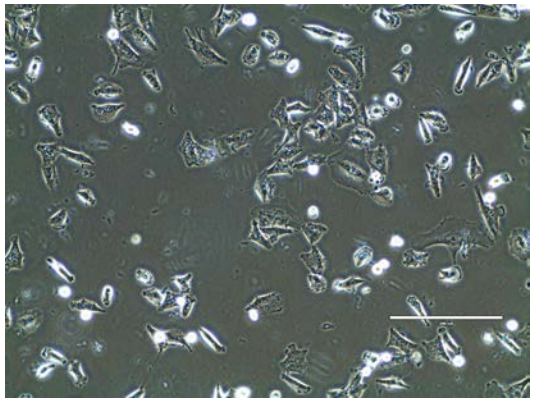
Results and Discussion

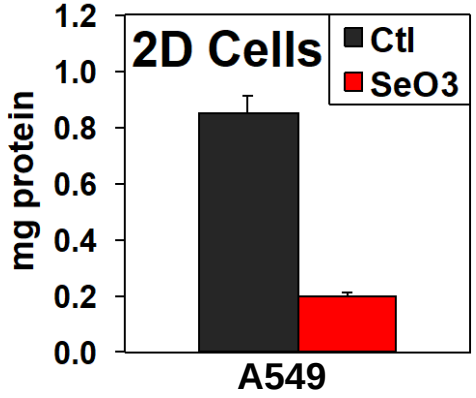
A549 spheroids are more resistant to SeO_3 than 2D counterparts

A549 Ctl

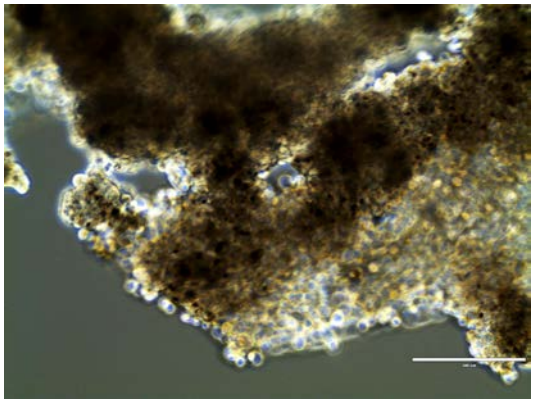


A549 SeO_3 (6.25 µM)

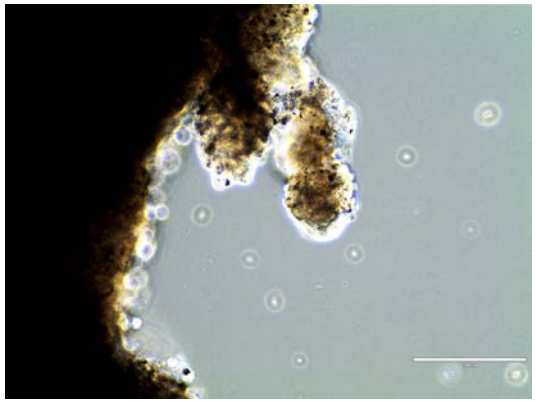


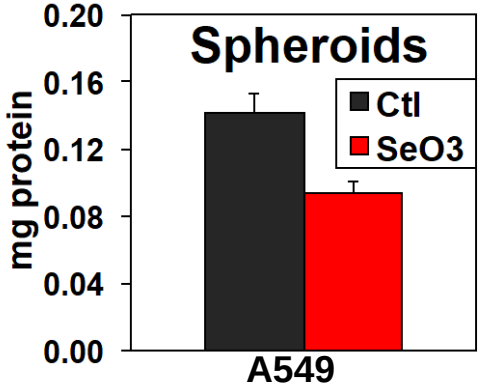


A549 Ctl

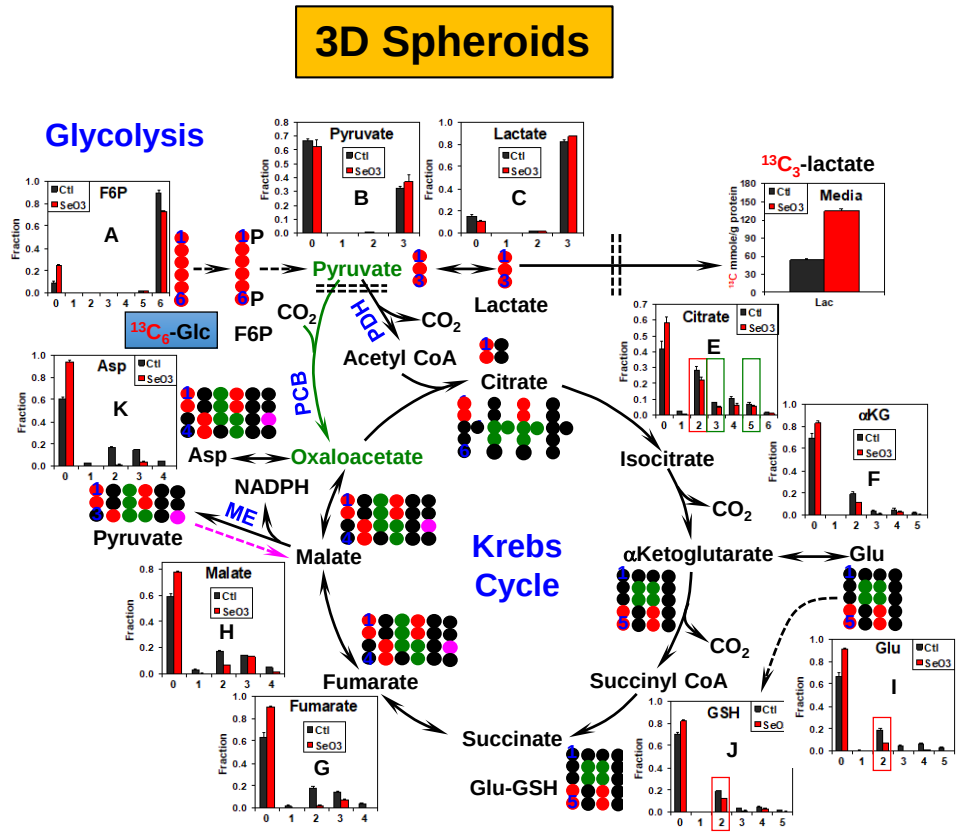


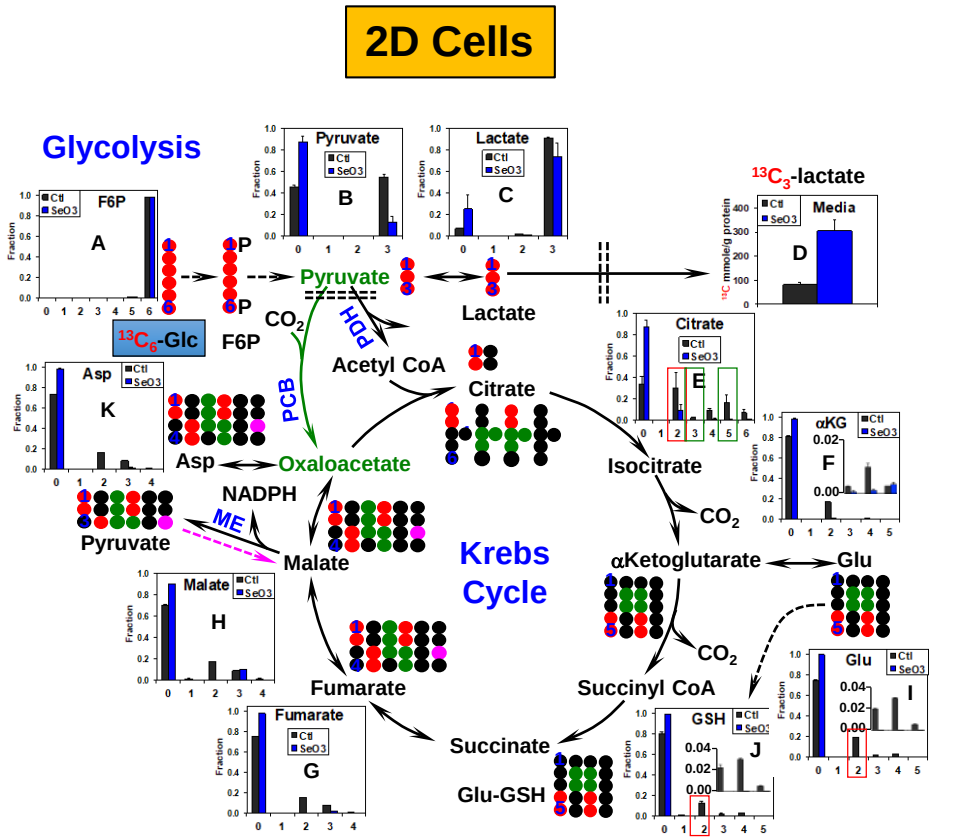
A549 SeO_3 (10 µM)



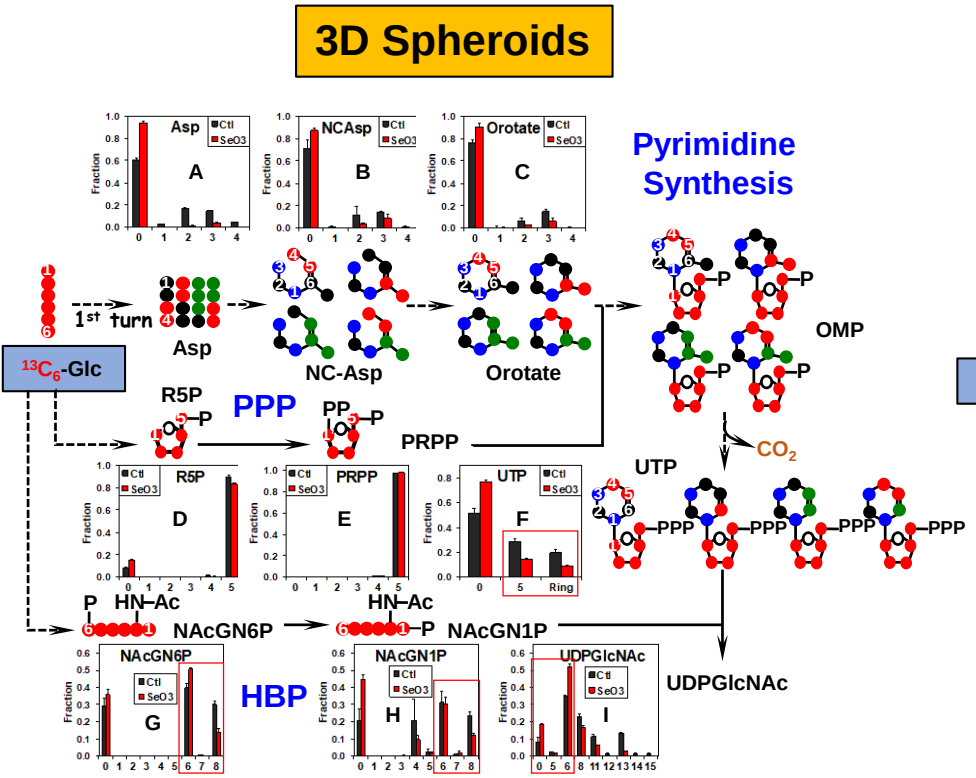


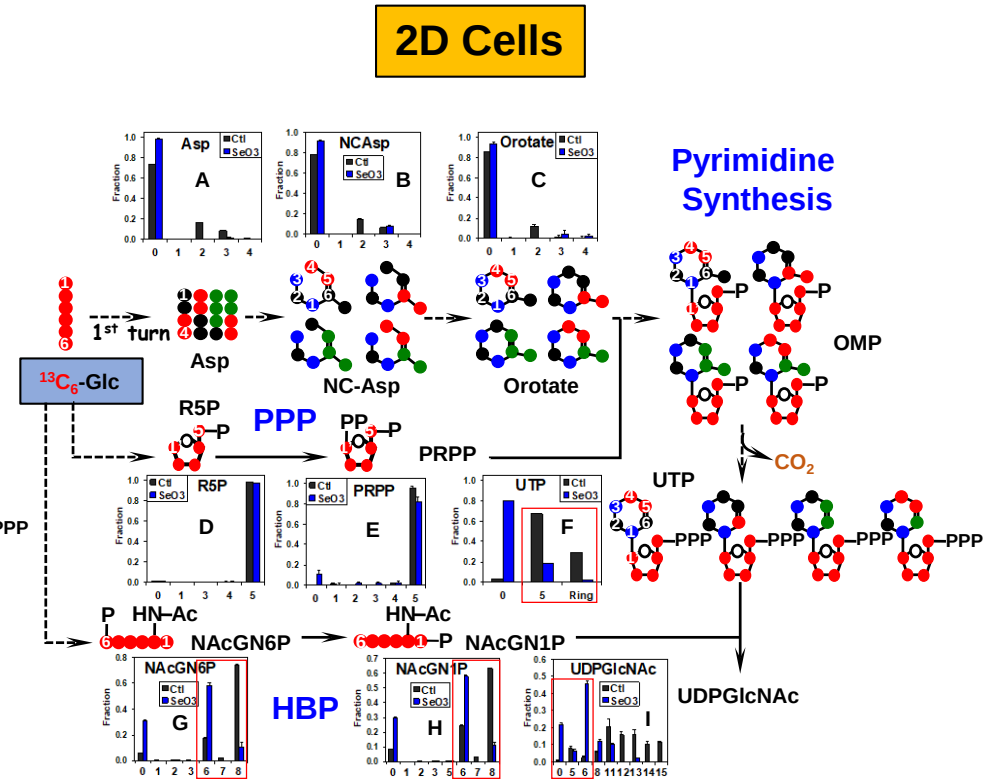
Glycolysis & the Krebs cycle were less impacted by SeO_3 in A549 spheroids than 2D counterparts





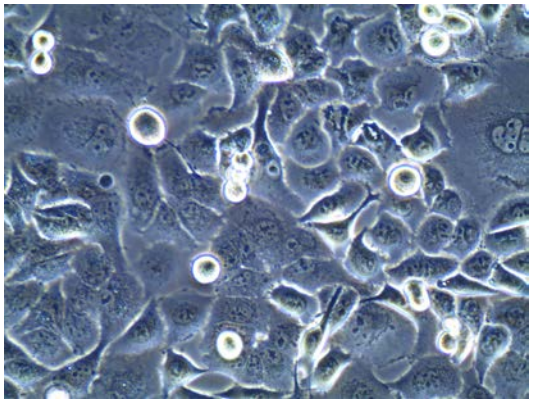
Pyrimidine & the hexosamine biosyn pathways (HBP) were less impacted by SeO_3 in A549 spheroids than 2D counterparts



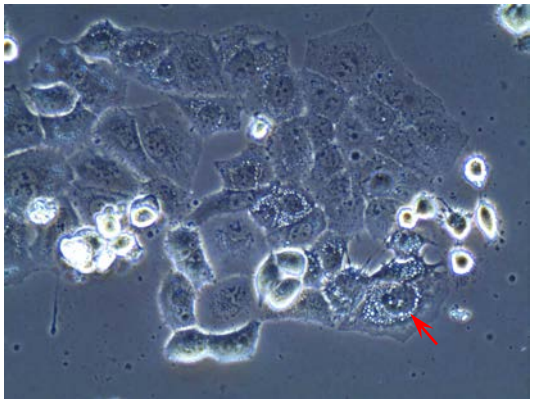


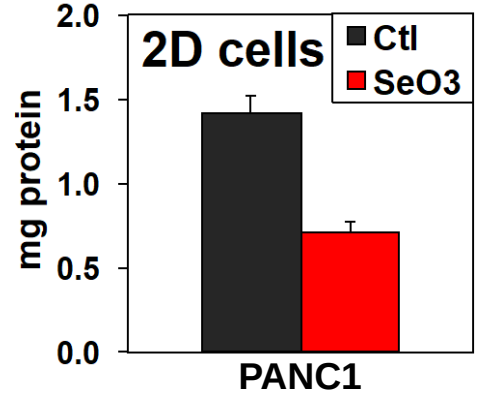
PANC1 spheroids are more resistant to SeO_3 than 2D counterparts

PANC1 Ctl

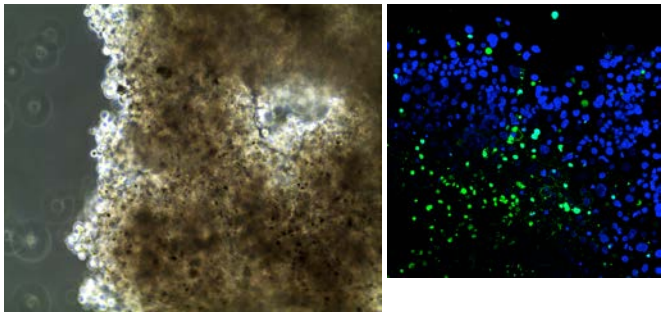


PANC1 SeO_3 (10 µM)

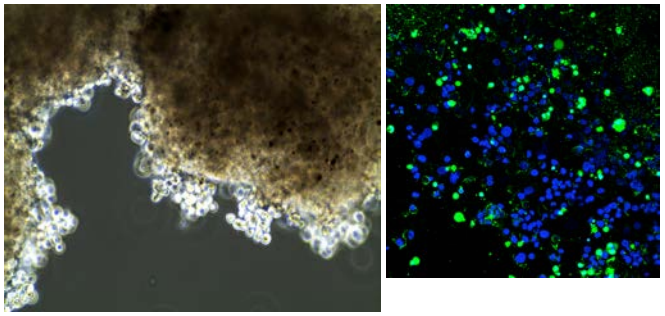


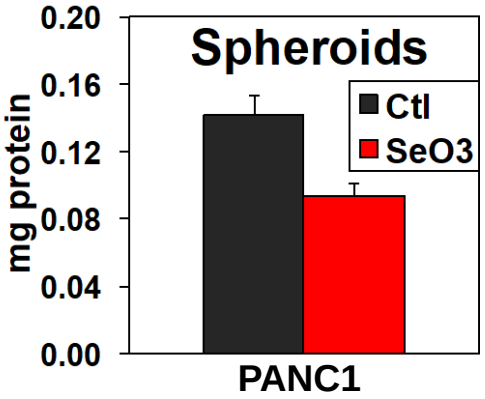


PANC1 Ctl

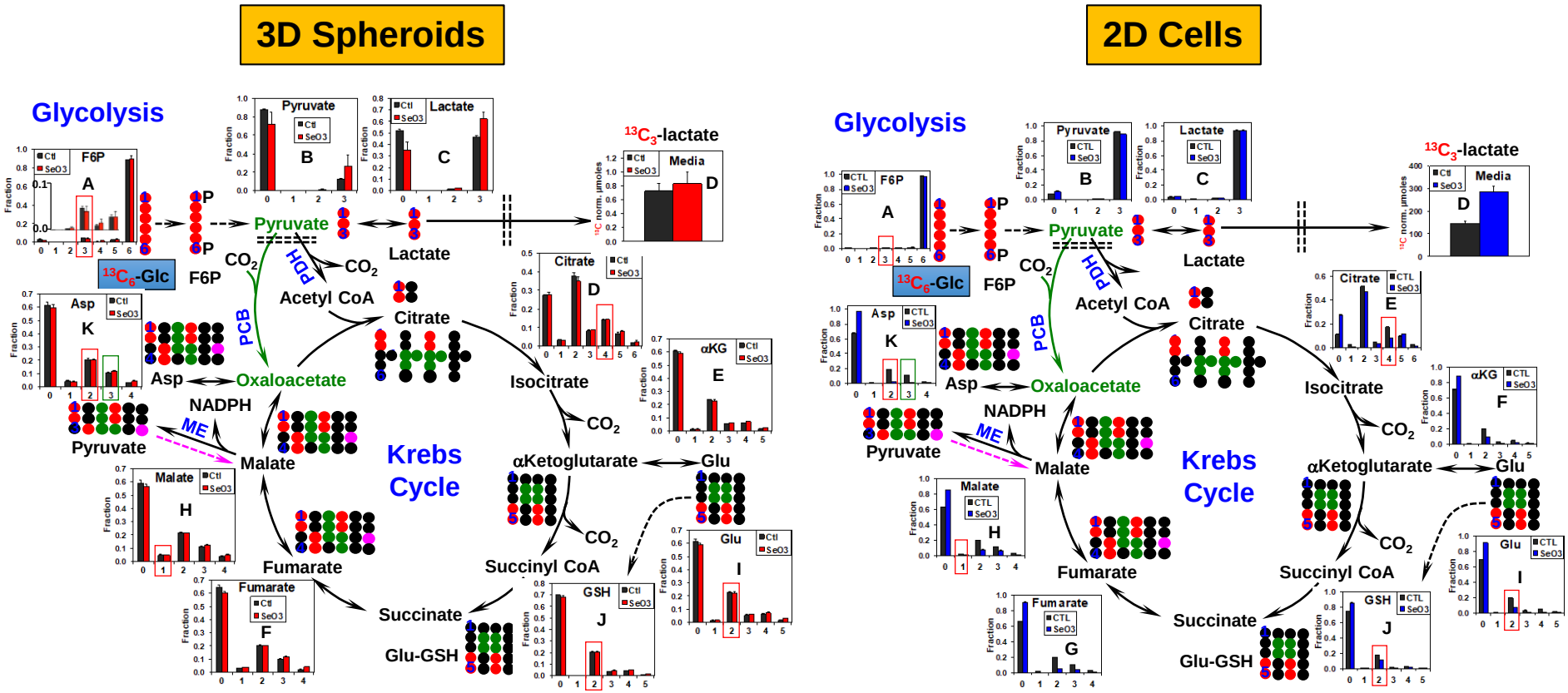


PANC1 SeO_3 (10 µM)



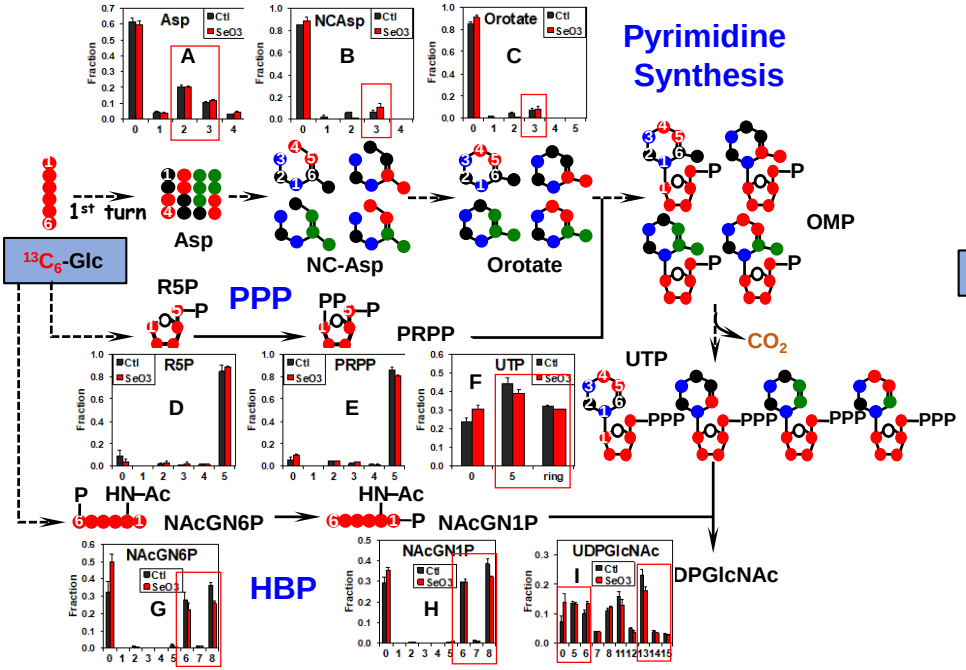


Glycolysis & the Krebs cycle were less impacted by SeO_3 in PANC1 spheroids than 2D counterparts

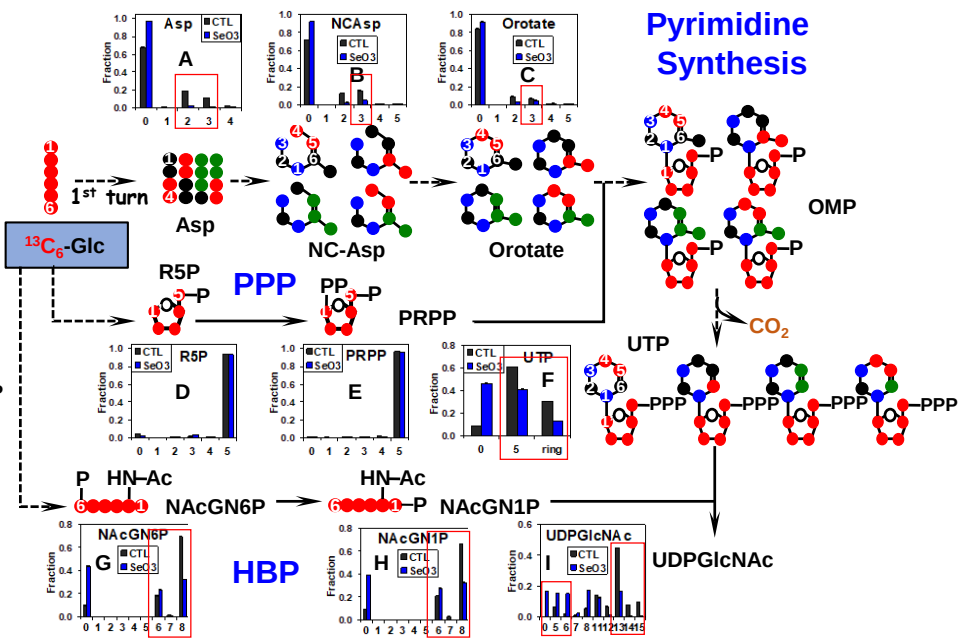


Pyrimidine & the hexosamine biosyn pathways (HBP) were less impacted by SeO_3 in PANC1 spheroids than 2D counterparts

3D Spheroids



2D Cells



Conclusions

- SIRM-mapped metabolic activity in M3DB spheroids was largely comparable to that in the 2D counterparts for both lung A549 and pancreatic PANC1 adenocarcinoma cell lines.
- A549 M3DB spheroids were more active in pyrimidine synthesis than the 2D counterparts.
- Gluconeogensis was active in PANC1 M3DB spheroids but not in 2D cell cultures.
- For both cell lines, M3DB spheroids were more resistant to anti-cancer SeO_3 treatment that the 2D counterparts in terms of growth.
- This drug resistance may be rooted in reduced sensitivity of M3DB spheroids to SeO_3 in glycolysis, the Krebs cycle, nucleotide synthesis, and glutathione metabolism, central to cell growth and survival.

Acknowledgments

- Yan Zhang, Hui Liu, Abagail L. Cornette, Qiushi Sun, and Richard M. Higashi
- Markey Foundation, & Kentucky Lung Cancer Foundation
- National Institute of Health (1P01CA163223-01A1, 1U24DK097215-01A1)