

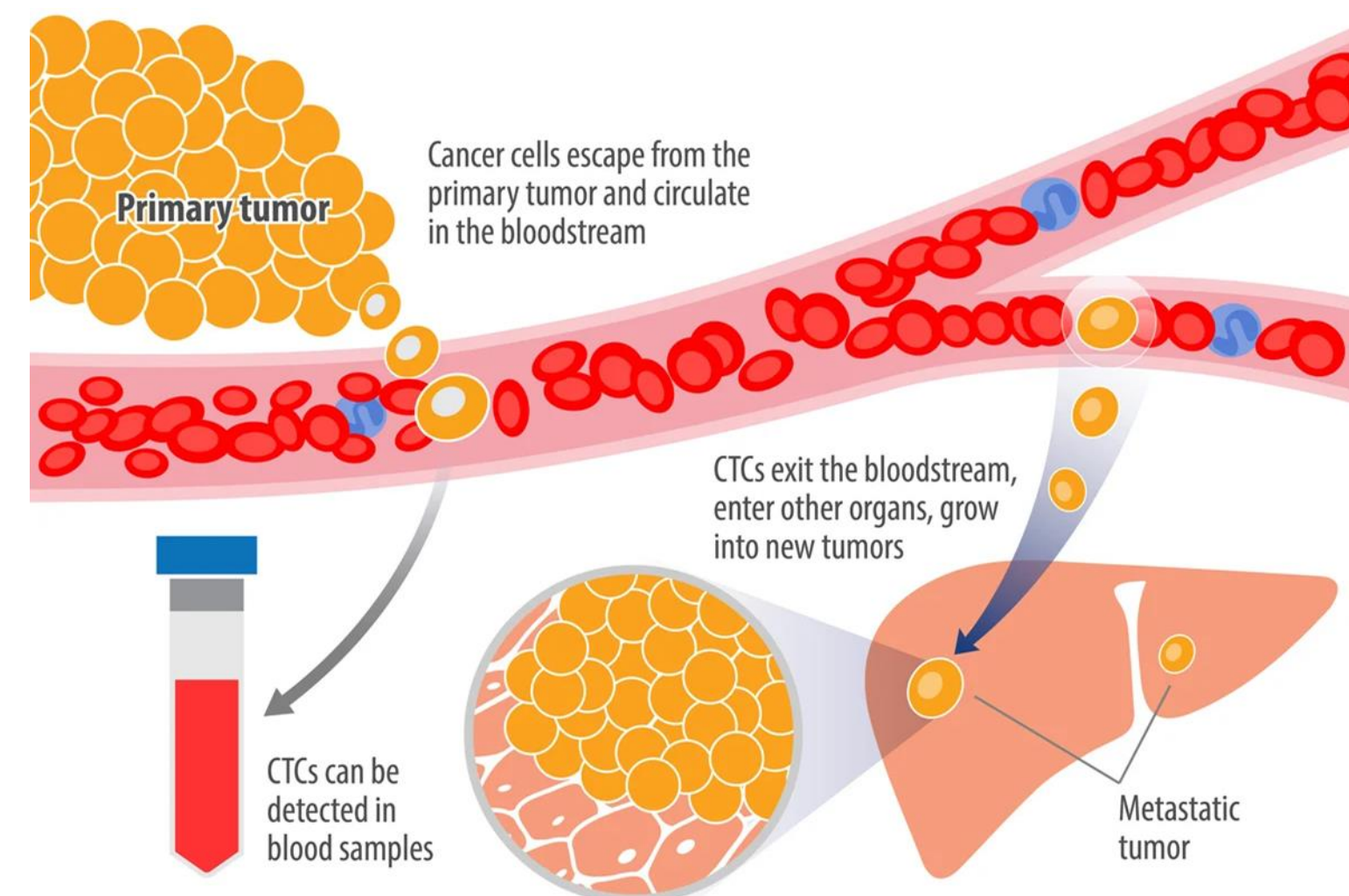
Lidocaine downregulates Src Kinase Activity in Pancreatic Cancer *in Vitro*

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Introduction

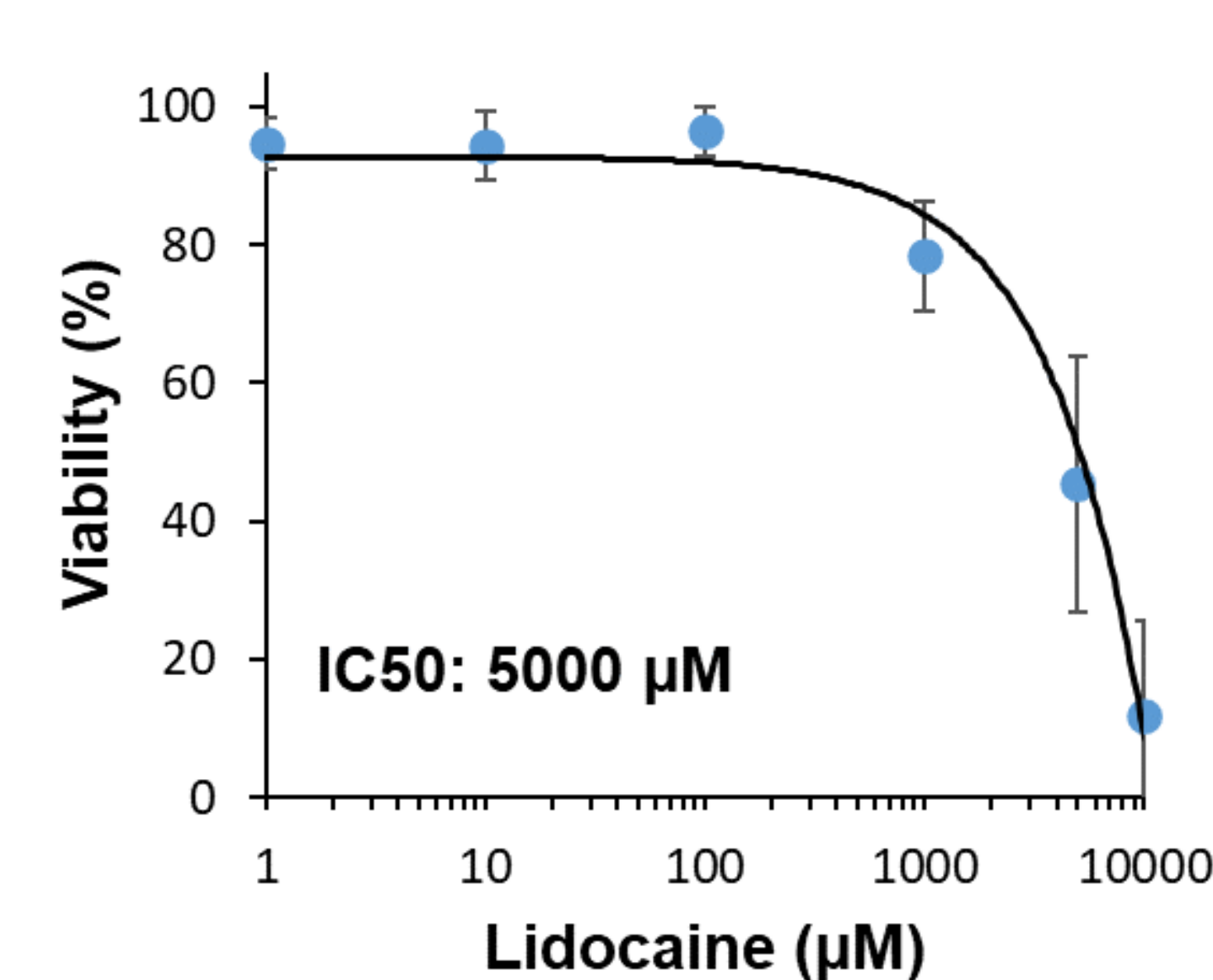
- Pancreatic ductal adenocarcinoma (PDAC) has a poor prognosis and is the 4th leading cause of cancer-related deaths
- Surgery is one of the main modalities of treatment, but release of circulating tumor cells (CTCs) due to surgical manipulation of the tumor may lead to metastasis
- Src protein tyrosine kinase is expressed significantly in PDAC and its elevated expression is related to tumor aggressiveness
- In vitro studies have shown that the amide local anesthetic lidocaine inhibits Src kinase expression in lung adenocarcinoma cells
- Goal:** Examine the effect of lidocaine on Src kinase activity in pancreatic adenocarcinoma cells



Methods

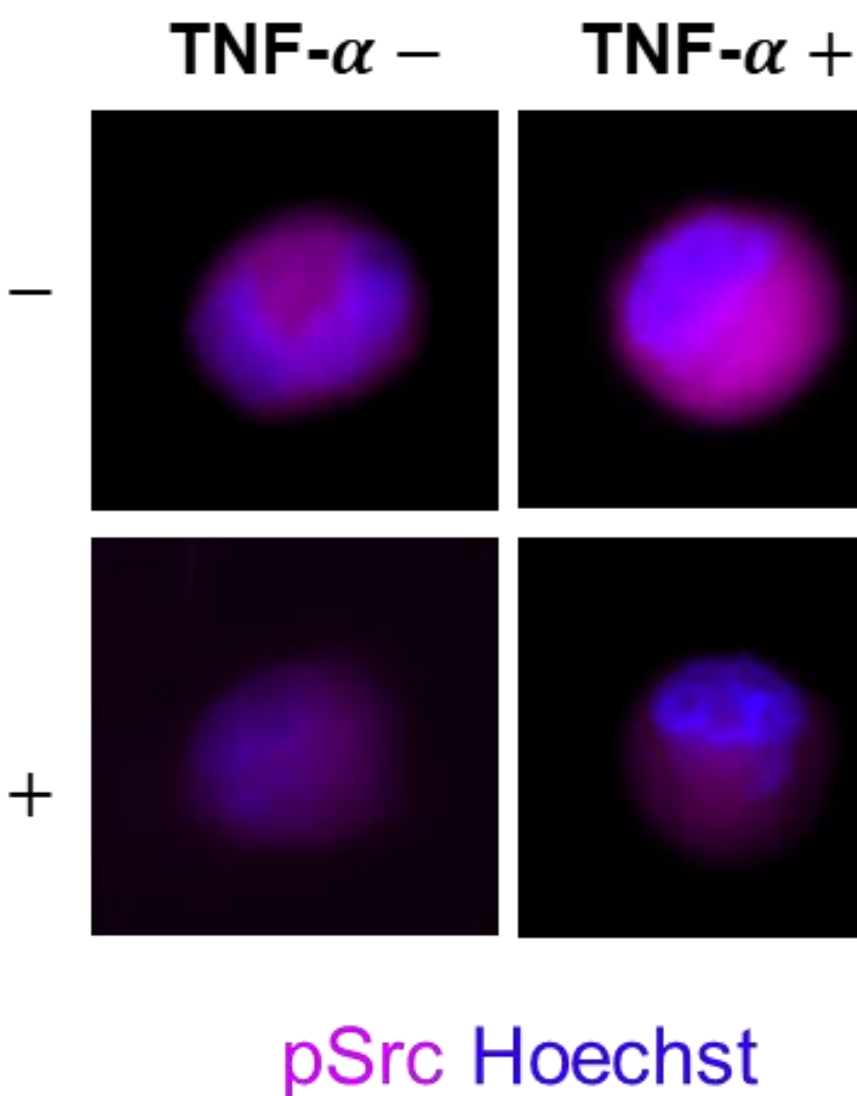
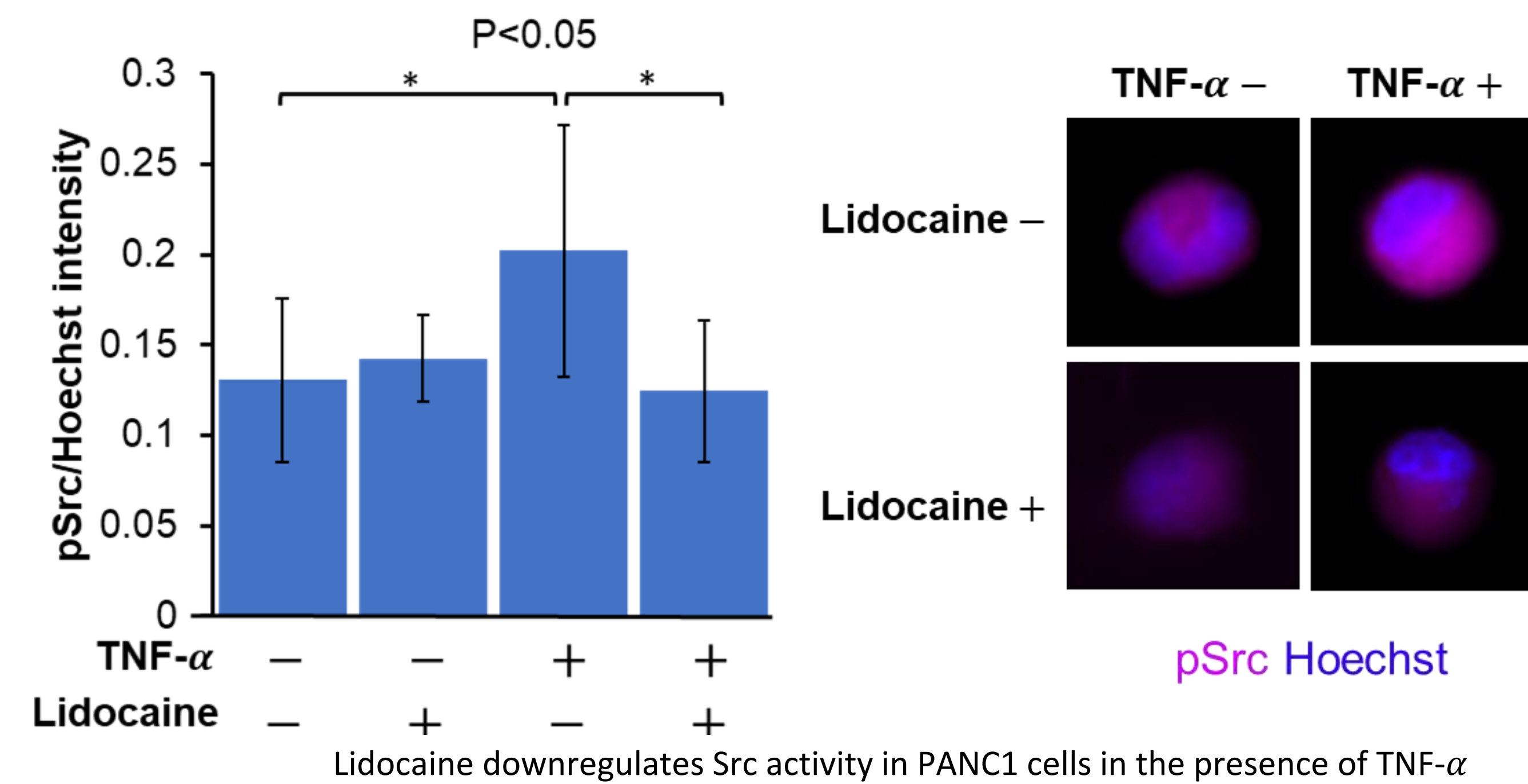
- Used pancreatic cell line PANC1
- Viability testing: cells treated with lidocaine (1 μM, 10 μM, 100 μM, 1000 μM, 5000 μM, and 10,000 μM in 1% FBS media) in 48-well plates and incubated (24hr, 37°C)
 - Cells then stained with Hoechst 33342 (1:1000) and Propidium Iodide (1:1000) to determine percentage of viable cells
- Seeded cells onto 48-well plate, incubated (20min) with or without 20 ng/mL TNF-α (mimics cancer environments)
- Cells treated w/ 10 μM lidocaine or 1% FBS media, incubated (30min)
- Cells immunostained for active phosphorylated (Tyr 418)-Src (pSrc)
- Cells also stained for nuclei with Hoechst 33342 as a standard
- pSrc expression intensity analyzed using ImageJ
- No patient identifiable information, so exempt from IRB review

Results



PANC1 cells maintain viability after lidocaine treatment in clinically relevant concentrations

- Exposure of clinically relevant concentrations of lidocaine for 24 hours yielded no adverse impact on the viability of PANC1 cells
 - High cell viability was maintained around 95% in 10-100 μM lidocaine
- In subset of PANC1 cells subjected to TNF-α, those treated with 10 μM lidocaine exhibited 60% the level of pSrc as non-lidocaine-treated counterparts (p<0.05)
- In absence of TNF-α, no statistically significant difference in pSrc levels observed between lidocaine-treated PANC1 cells and untreated counterparts
- Quantitative analysis of Src kinase activity in both control and lidocaine-treated PANC1 cells was conducted by assessing the ratio of fluorescence intensity of nuclei to cellular pSrc



Discussion

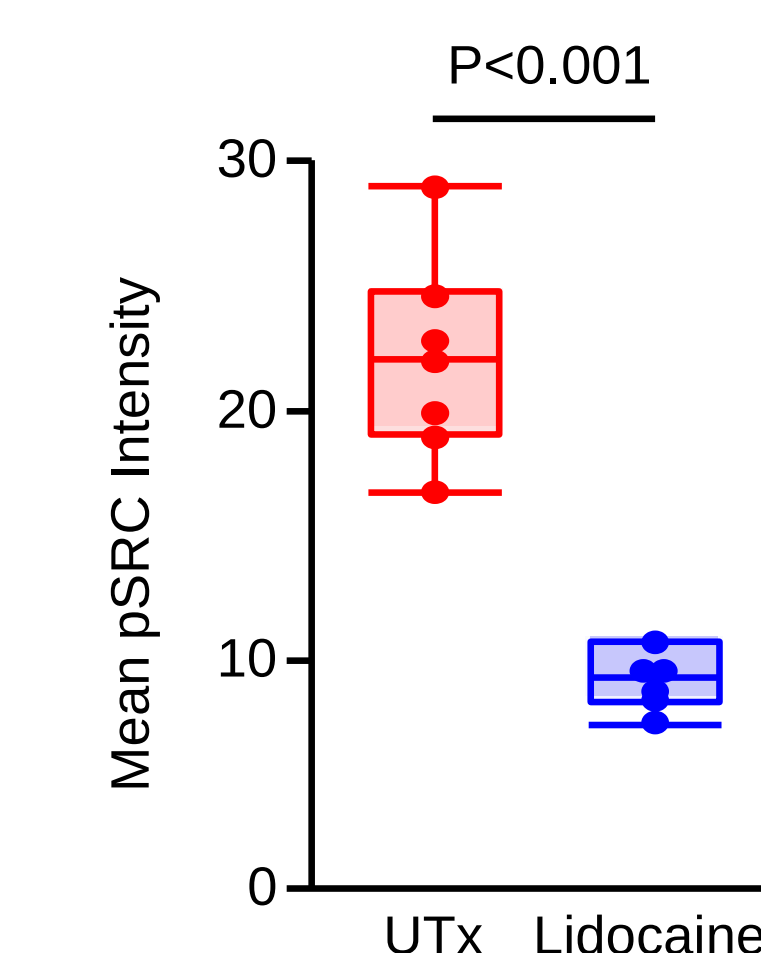
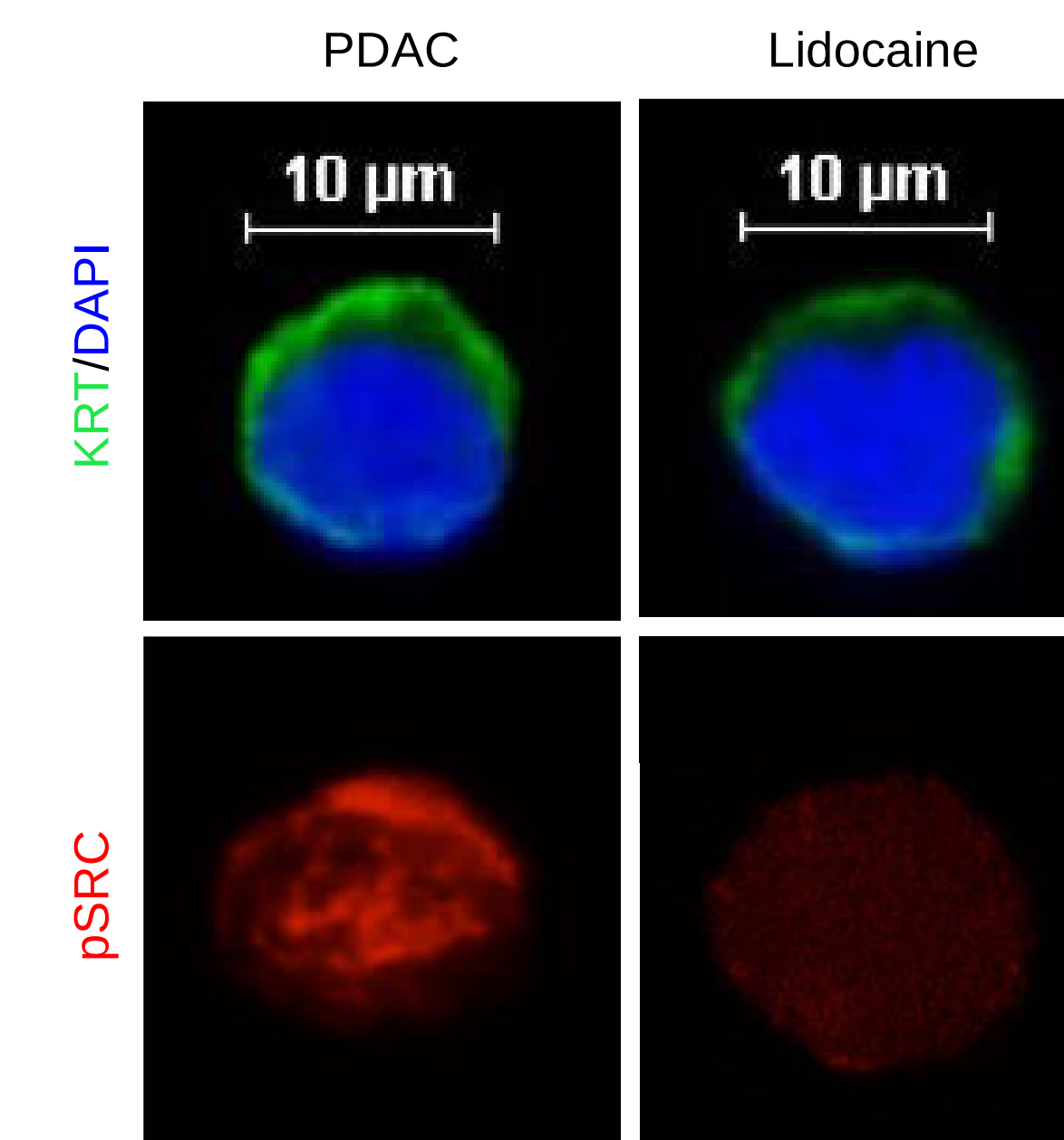
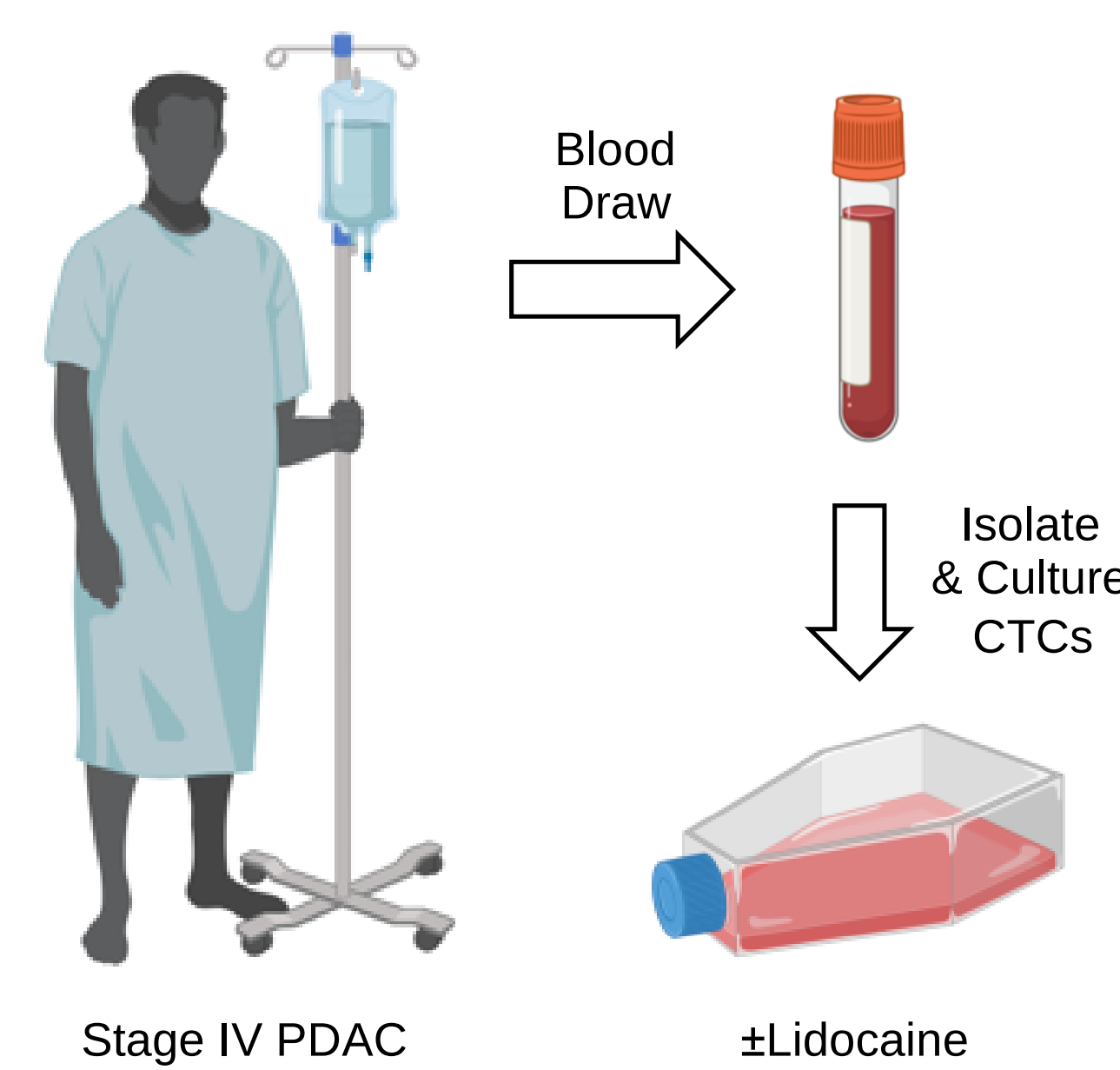
- Our investigation has established a substantial reduction in cellular pSrc levels in PANC1 cells exposed to TNF-α and subsequent lidocaine treatment
- These findings suggest that lidocaine, administered at therapeutic concentrations, holds the potential to effectively inhibit TNF-α-dependent Src activity
- Previous studies have indicated that Src may also regulate tissue remodeling and degradation of the extracellular matrix in pancreatic cancer cells
- It has been postulated that Src inactivation could suppress cellular invasiveness, including the inhibition of cellular motility and alterations in cell-cell and cell-extracellular matrix interactions
- Our research is extending the scope of this study to pancreatic cancer patients undergoing surgical interventions
 - We are applying our methods to study the effect of lidocaine infusions on pancreatic cancer patients diagnosed with PDAC undergoing surgery
 - These studies will provide valuable insights into the clinical applicability of lidocaine in modulating cancer-related processes and may affect the anesthetic management of cancer patients undergoing surgery

Acknowledgement

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References

- Ito, Hiromichi, James Gardner-Thorp, Michael J. Zinner, Stanley W. Ashley, and Edward E. Whang. "Inhibition of Tyrosine Kinase Src Suppresses Pancreatic Cancer Invasiveness." *Surgery* 134, no. 2 (August 2003): 221–26.
- Piegeler, Tobias, E. Gina Votta-Velis, Guoquan Liu, Aaron T. Place, David E. Schwartz, Beatrice Beck-Schimmer, Richard D. Minshall, and Alain Borgeat. "Antimetastatic Potential of Amide-Linked Local Anesthetics." *Anesthesiology* 117, no. 3 (September 1, 2012): 548–59.
- Pimenta, Michael, Mouad Edderkaoui, Ruoxiang Wang, and Stephen Pandol. "The Potential for Circulating Tumor Cells in Pancreatic Cancer Management." *Frontiers in Physiology* 8 (June 2, 2017): 381.
- Zhang, Caihui, Cuiyu Xie, and Yao Lu. "Local Anesthetic Lidocaine and Cancer: Insight Into Tumor Progression and Recurrence." *Frontiers in Oncology* 11 (June 24, 2021): 669746.
- Bourre, Ludovic. "Circulating Tumor Cells in Preclinical Mouse Models of Metastasis." *Crown Bioscience*. (August 20, 2019): web.



Lidocaine reduces Src phosphorylation in circulating tumor cells in human PDAC