Cell-retraction pumping: A new cancer target?
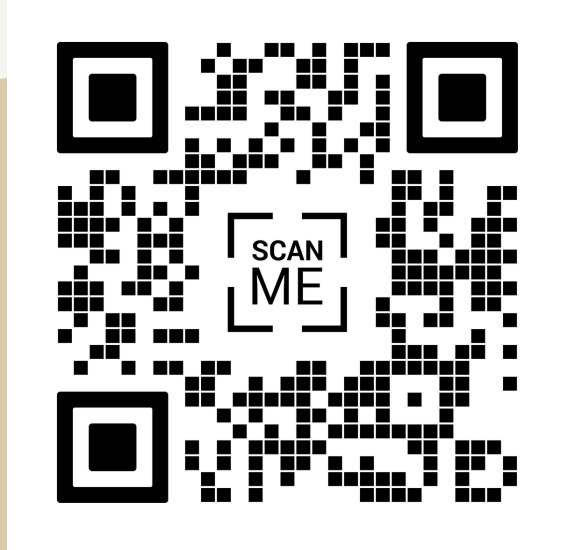
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Introduction

Cancer resistance to chemotherapy is driven by cancer cell diversity. We previously discovered that fibroblasts inject cytoplasm *via* cell-projections into cancer cells which increases cancer cell diversity. We labelled this cell-projection pumping (CPP). We now consider if whole-cell retraction could have the same effect by exploring the concept of cell-retraction pumping (CRP). If so, improving chemotherapy will need two strategies, one to block CPP, and another to block CRP. All data required to model CRP is available, except clairty on whether cell retractions occur globally or are localised to specific regions. We use cutting-edge technology, single-cell tracking, and computer shape analysis, to answer this key question.
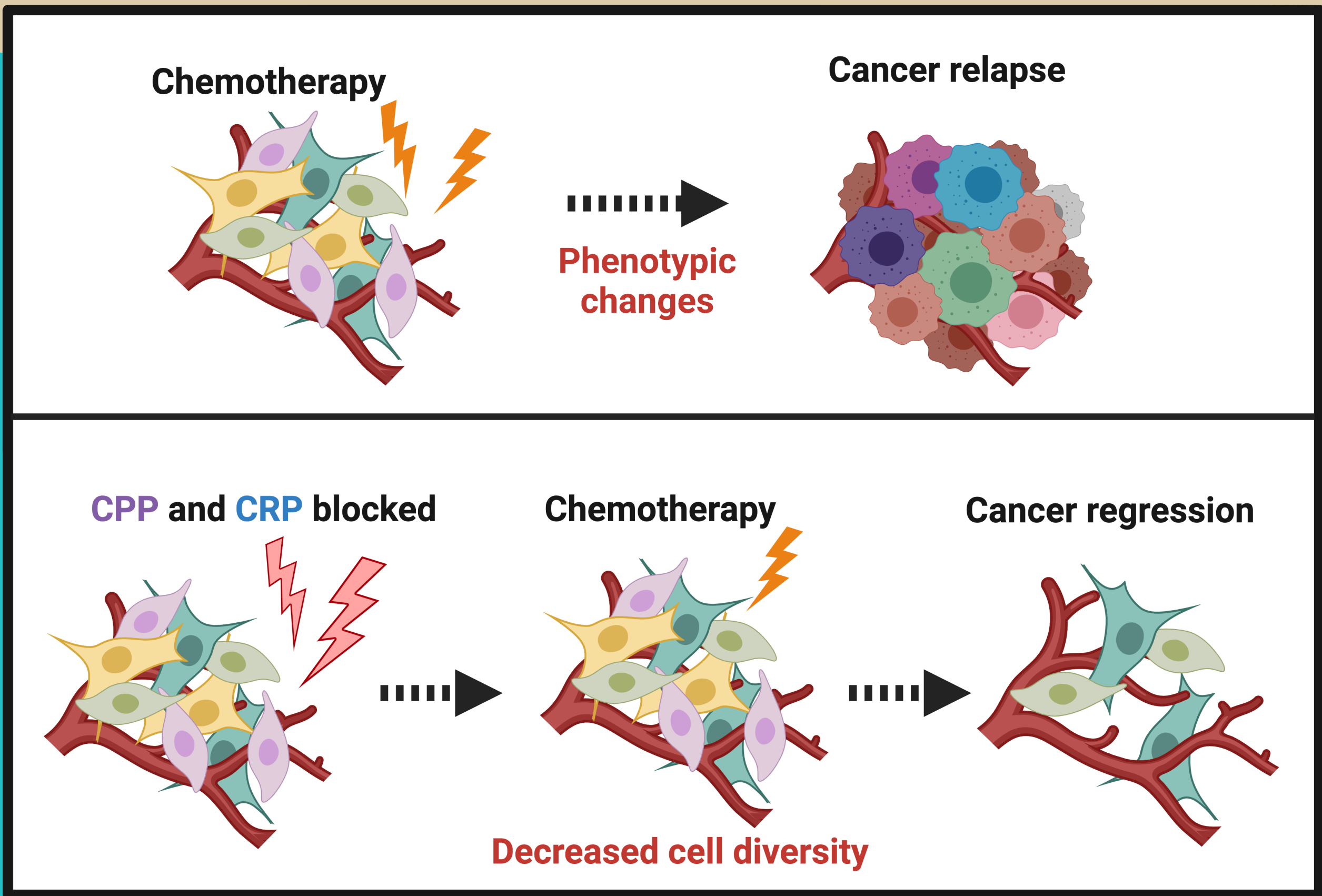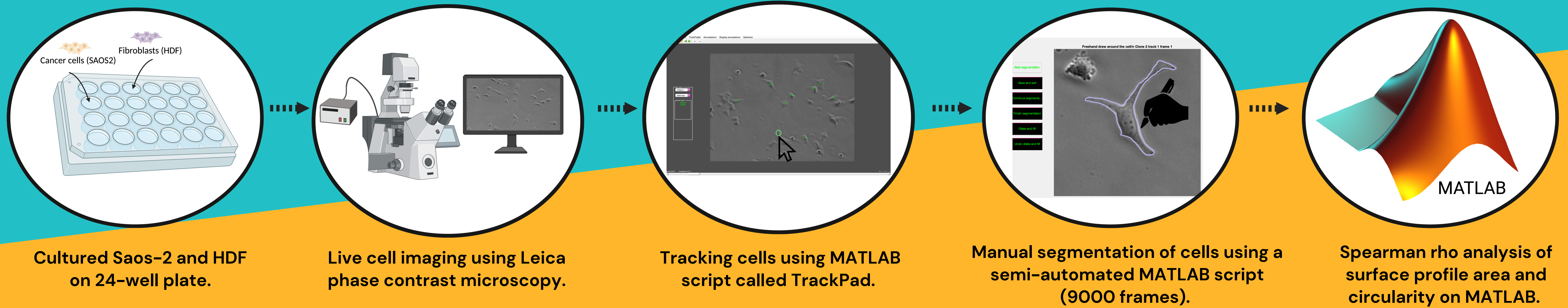

Figure 1: A) Motive force of cell-projection pumping. B) Motive force of cell-retraction pumping.

Figure 2: Cancer cells change their phenotype to resist chemotherapy. Blocking CPP and CRP will be a useful adjunct therapy to prevent this.

Hypothesis and Aims

H: Cells change shape more by extending and retracting local parts of the cell, rather than generalised contractions.

A1: To measure shape changes in osteosarcoma Saos-2 and human dermal fibroblast (HDF) cell lines over time.

A2: To consider critical parameters for a mathematical model that would estimate pressure changes which drive CRP.

Research Plan

Cultured Saos-2 and HDF on 24-well plate.

Live cell imaging using Leica phase contrast microscopy.

Tracking cells using MATLAB script called TrackPad.

Manual segmentation of cells using a semi-automated MATLAB script (9000 frames).

Spearman rho analysis of surface profile area and circularity on MATLAB.

Results

Trends in cell surface profile area and circularity indicate shape change happens in localised regions. Validated by Spearmans Rho analysis.
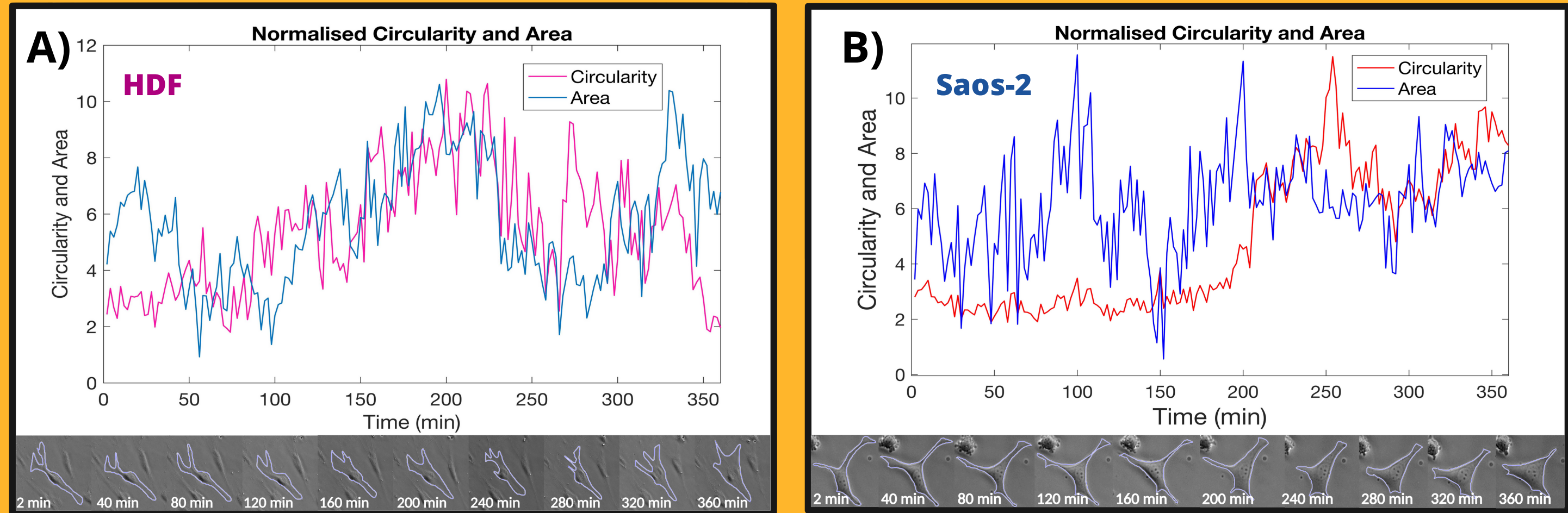

Figure 3: Normalised area and circularity for HDF (A) and Saos-2 (B) of one cell cultured in isolation 6 hours.
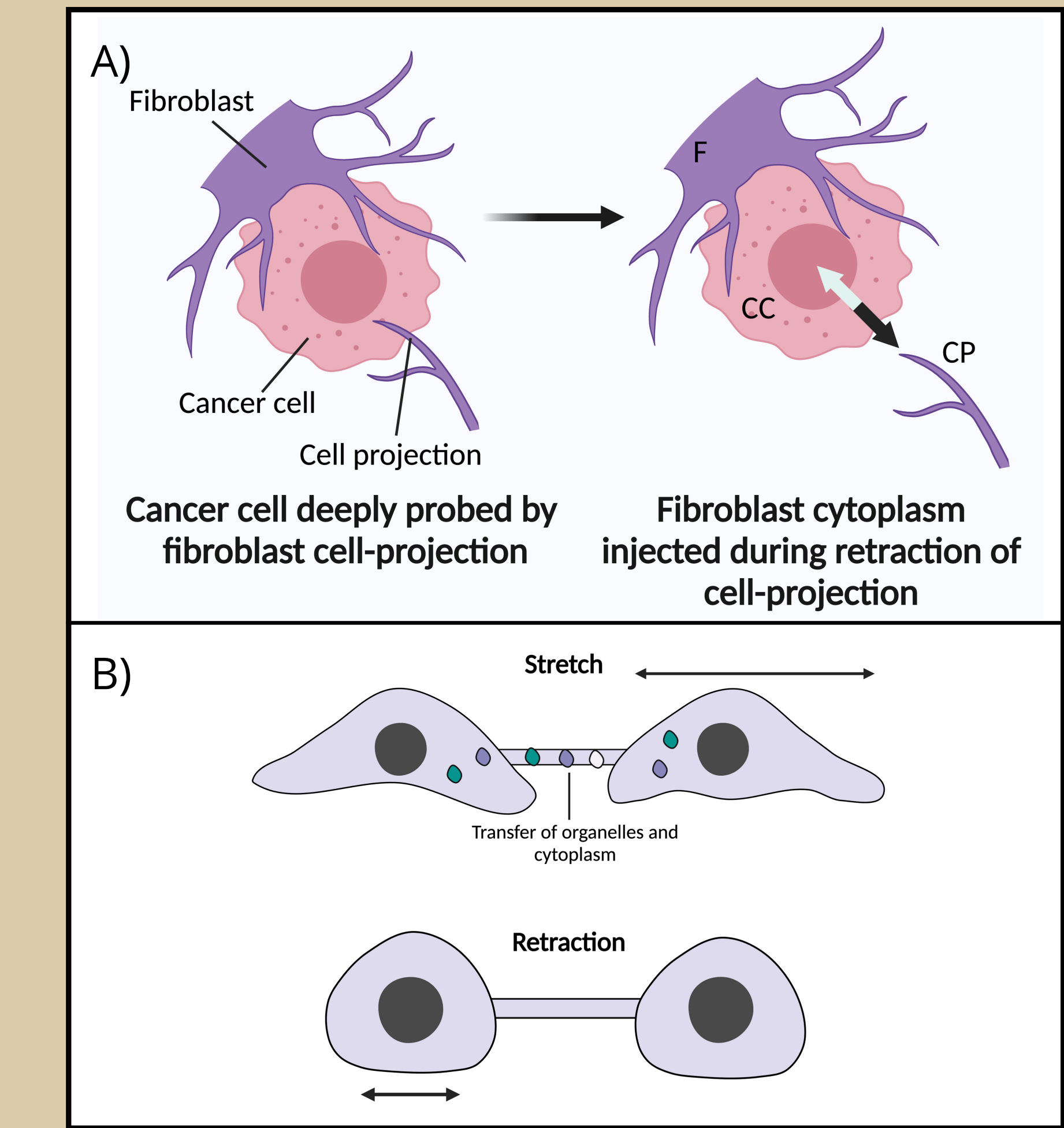
Conclusions

Establishing how shape change happens will allow us to construct a mathematical model to explore CRP.

Model of fibroblast and cancer cell permits us to address fundamental questions impossible to approach in the entire complexity of a living organism.

Future direction: propose an initial mathematical model to account for cytoplasmic transfer via CRP and explore CPP/CRP in 3D co-cultures.

Significance

Figuring out if CRP occurs will advance our understanding about how fibroblasts cause cancer cells to change their phenotype and resist chemotherapy.

[1] Zoellner, H., Paknejad, N., Cornwell, J., Chami, B., Romin, Y., Boyko, V., Fujisawa, S., Kelly, E., Lynch, G., Rogers, G., Manova, K. and Moore, M., 2020. Potential Hydrodynamic Cytoplasmic Transfer between Mammalian Cells: Cell-Projection Pumping. Biophysical Journal, 118(7), p.1795.