

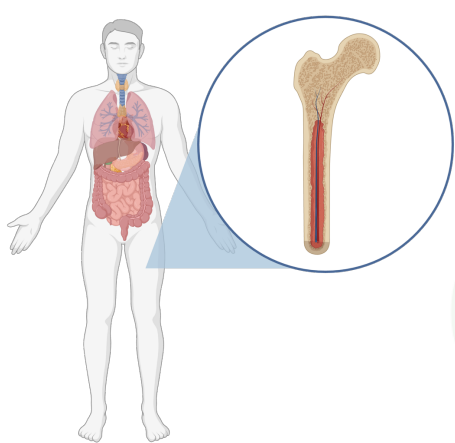
# Bioengineered human leukaemia organ on chip model for drug development.

Authors: Celia Ribes Balanza<sup>1</sup>, Savvas Ioannou<sup>1</sup>, Manuel Salmeron-Sanchez<sup>1,2</sup>, Matthew J Dalby<sup>1</sup>, Hannah Donnelly<sup>1</sup>

<sup>1</sup>Centre for the Cellular Microenvironment, University of Glasgow

<sup>2</sup>IBEC, Universitat de Barcelona

## 1. Introduction.



- The bone marrow is a specialised microenvironment that controls and regulates blood production.
- Leukaemia is a blood cancer affects 10,300 people in the UK annually with only a 41% survival rate and arises from mutations in haematopoietic stem cells (HSCs)

Nestin positive mesenchymal stromal cells (MSCs) secrete stem cell factor (SCF) which promotes quiescence and survival (Figure 1A) of HSCs. HSCs spatially home near nestin positive MSCs (Figure 1B)

Leukemic cells remodel the bone marrow to favour their survival but current *in vitro* models do not consider or recreate this. Here we investigate this remodelling.

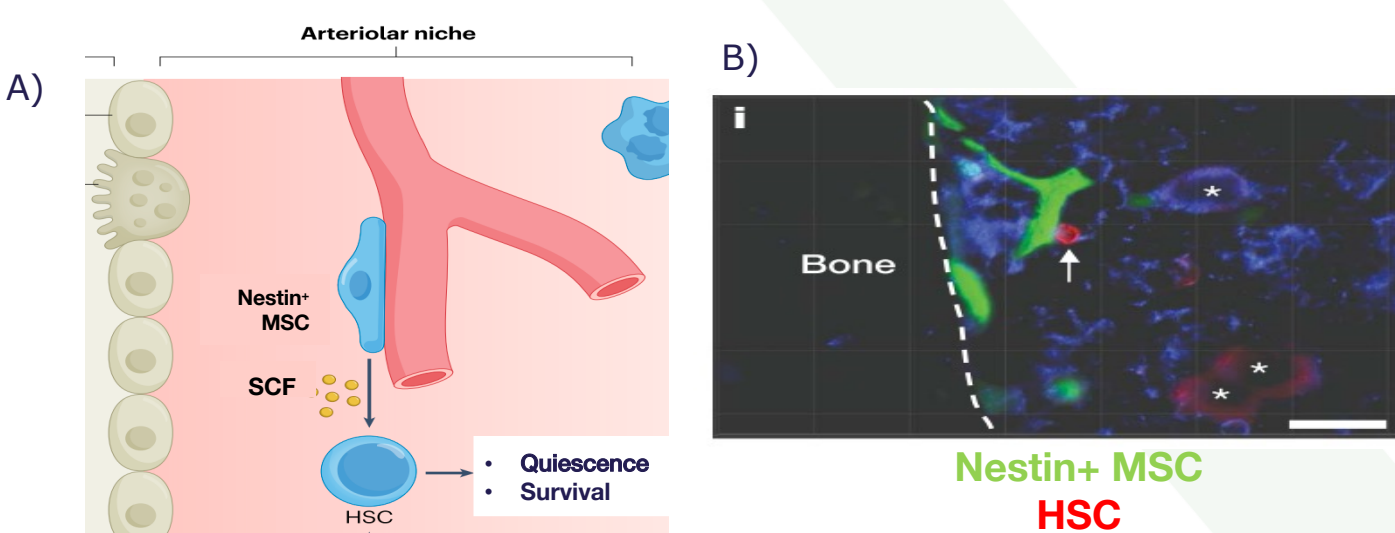


Figure 1A. Importance of stem cell factor (SCF) for haematopoietic stem cell (HSC) maintenance and survival. Adapted from Rogkoti et al., Nature Reviews Bioengineering, 2025. B) Mesenchymal stromal cell (MSC) and haematopoietic stem cells (HSCs) spatial location in the bone marrow. Adapted from Mendez-Ferrer et al., Nature, 2010

## 2. Methods.

Biological-synthetic hybrid hydrogels made from polyethylene glycol (PEG) maleimide functionalised with full-length fibronectin (FN) of tuneable stiffness are used to create our 3D model (Figure 2A).

The stiffness mimics that of the bone marrow which ranges from 250-24700 Pa (Figure 2B).

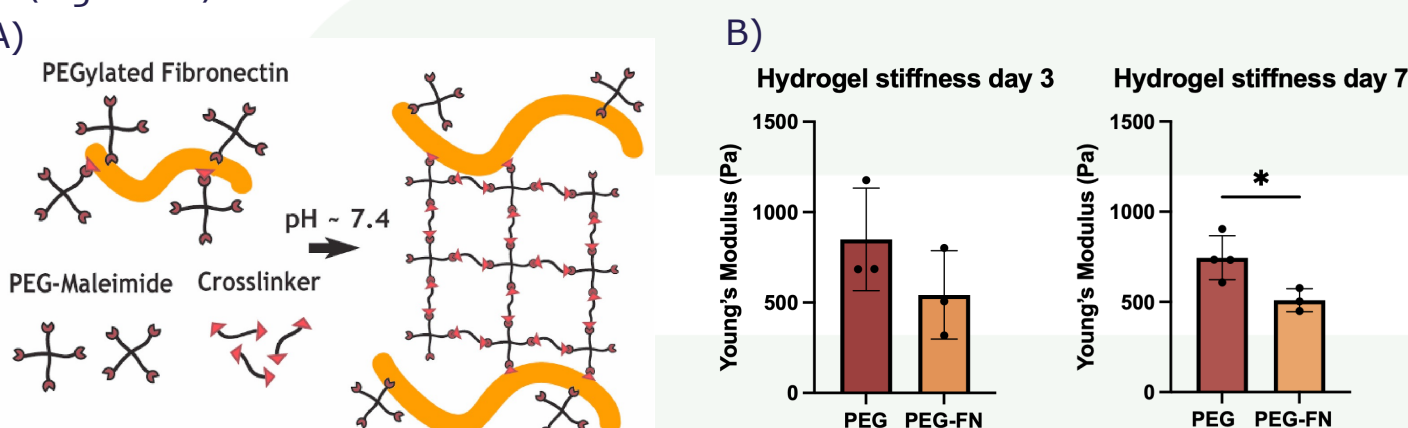


Figure 2A. Adapted from Trujillo et al., Biomaterials, 2020. B) hydrogel stiffness measured with rheology

Human primary MSCs were spheroided (Figure 3A) and embedded into the hydrogels with or without acute myeloid leukaemia (AML) cells (Figure 3B)

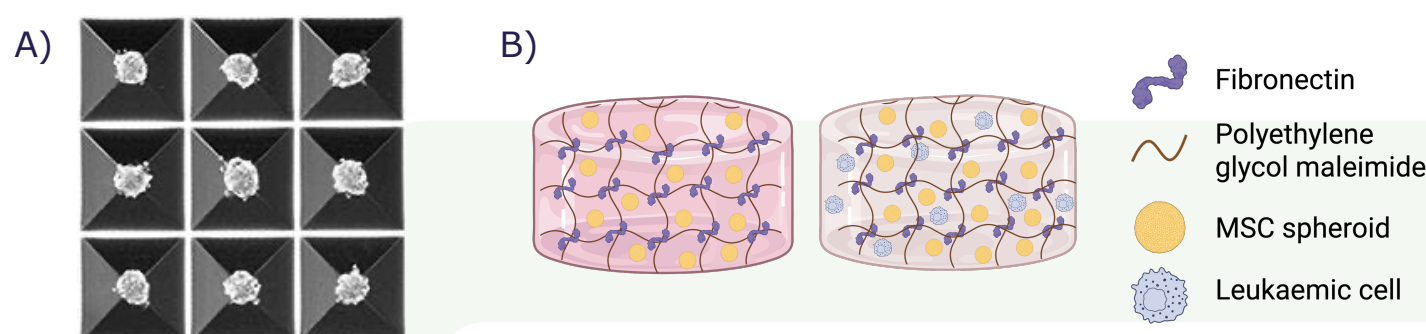


Figure 3A. Mesenchymal stromal cell (MSC) spheroids. B) Healthy and leukaemic hydrogels

## 3. Leukemic remodelling of the niche.

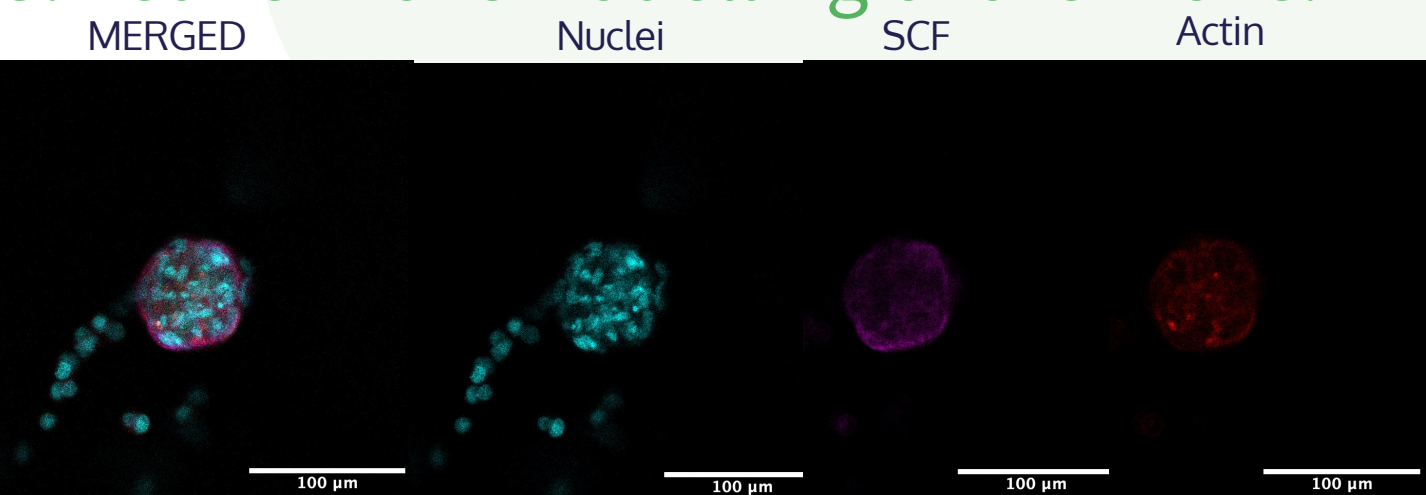


Figure 4A. Mesenchymal stromal cell spheroids (MSCs) with leukaemic cells. Stem cell factor (SCF)

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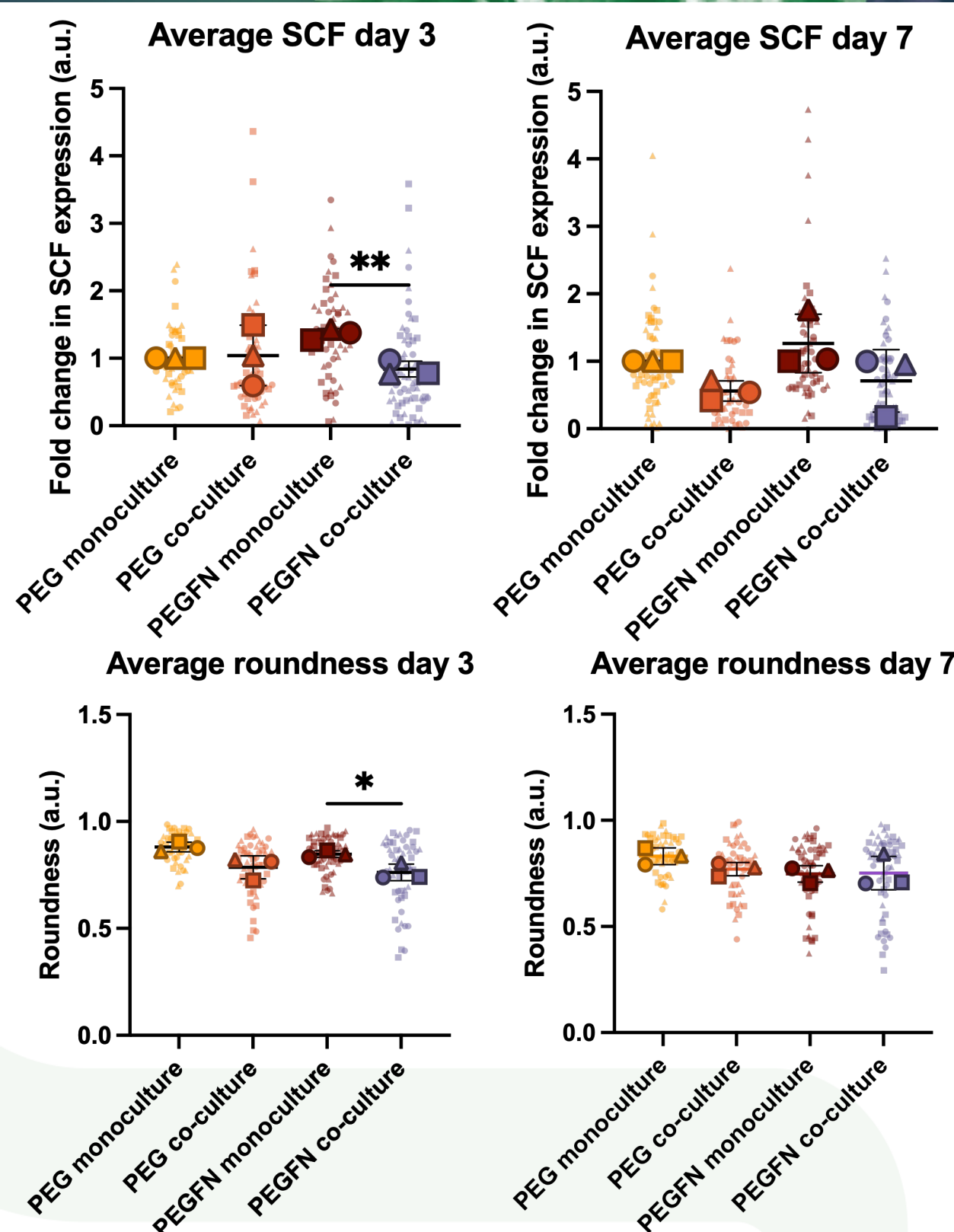


Figure 5. Phenotype and morphology measurements on mesenchymal stromal cell spheroids in hydrogels. Stem cell factor (SCF). Polyethylene glycol (PEG). PEG fibronectin (PEGFN), n=3

## 5. Niche support of leukemic cells

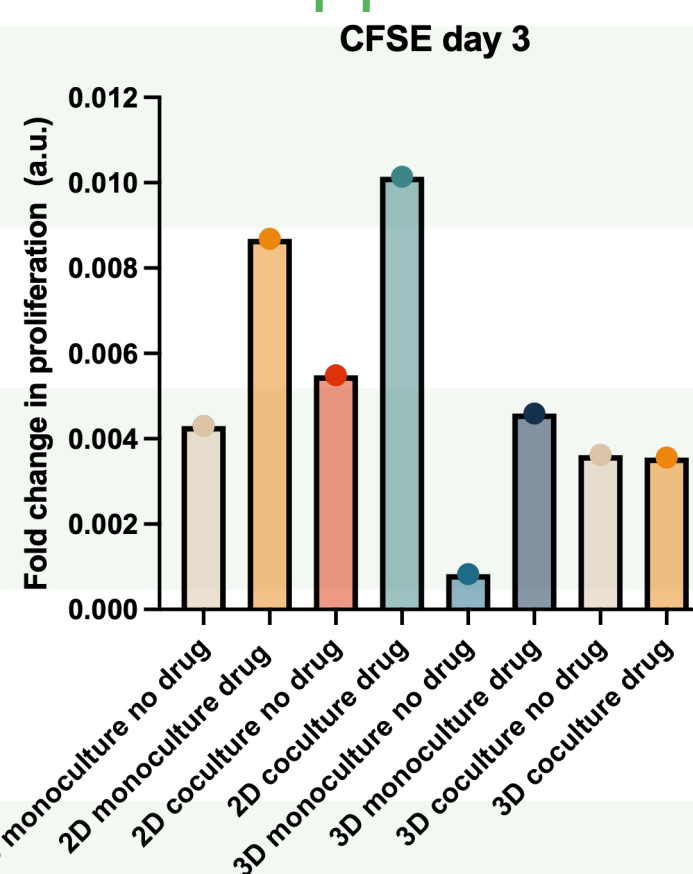


Figure 6. Proliferation of leukemic cells in monoculture and co-cultured with mesenchymal stromal cell spheroids in polyethylene glycol fibronectin hydrogels, n=1

- Leukemic proliferation in 2D and 3D monoculture and co-culture with MSCs, with and without cytarabine.
- Cytarabine – DNA polymerase inhibitor
- High fold change = less proliferation

## 6. Future work.

- Leukaemia on chip
- Leukemic bone marrow and secondary lymphoid site connected by microfluidic channels
- Investigate leukaemic infiltration and target it pharmacologically

