Goodbye flat biology

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What is the problem?

Blood cancer, also called leukaemia, is the 5th most common type of cancer. In leukaemia, the normal production of blood cells in the bone marrow is impaired, and white blood cells (which protect us from infections) out compete red blood cells (which carry oxygen round our bodies) and platelets (which regulate blood clotting). Without the right amount of normal blood cells, your body's organs and tissues will not get the oxygen they need to work properly, and your body won't be able to fight off infection or clot blood when needed. Blood cancer is partly manageable with chemotherapy (anti-cancer drugs), but many patients rely on treatment for the rest of their lives, which is associated with adverse side effects of the drugs. Patients may also develop resistance to treatments, so the drugs no longer work.

What are we interested in?

We are interested in discovering new ways of targeting leukaemic cells and have found in the past that the 'BMP' pathway is altered in patients who are resistant to treatment, making it an interesting therapeutic target. We now want to test known BMP inhibitors and evaluate their effectiveness against leukaemic cells.

When testing new drugs, we historically use systems of cells grown in the lab in 2 dimensions (2D) but these 2D systems do not represent the bone marrow well. We are working on new 3D models which we hope will be better models. They are made of various cell types of the bone marrow microenvironment and mimic its architecture by using collagen - the most abundant protein in the bone marrow. These models can then be used to test new, targeted therapies in a more realistic way and hopefully help to reduce animal testing.

What did we do?

We worked on different ways of forming spheroids (3D clusters) of mesenchymal stem cells (MSCs), which are cells with the potential to form bone, fat or cartilage (a connective tissue) and are known to help leukaemic cells to evade treatment. We either used magnetic nanoparticles (tiny particles) (see Figure 1A) or microfluidic devices (see Figure 1B) to produce spheroids. The spheroids formed with our magnetic nanoparticles can be transferred into collagen and leukaemic cells grown on top of the collagen, enabling us to study the leukaemic cells' migration behaviour towards MSCs and the effect of BMP inhibitors.

Microfluidics is a branch of science that deals with tiny quantities of liquids and in our microfluidic devices we form many spheroids at the same time and directly treat the cells with the BMP inhibitors within the microfluidic device. However, the addition of collagen is currently not possible, so the microfluidic model does not represent the bone marrow as well.

Our first experiments involved treating the spheroids in microfluidic devices with various drugs, including BMP pathway inhibitors, and examining the viability of the non leukaemic cells, as we want to ensure we are not damaging cells other than our intended leukaemic cells. Secondly, we tested the ability of leukaemic cells to migrate through the collagen in our nanoparticle-based model as direct leukaemic cell-MSC contact is crucial during treatment and patient resistance to therapies.

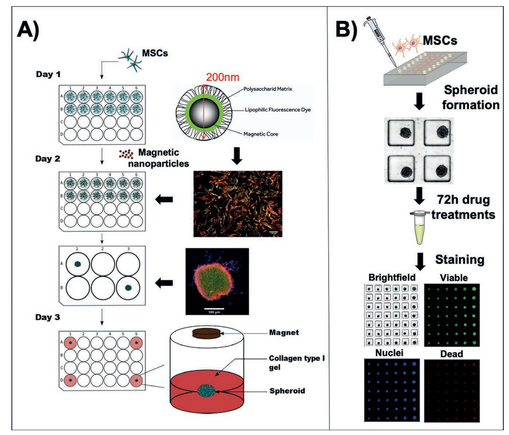

Figure 1 Schematic representation of spheroid formation using a nanoparticle **(A)** or microfluidics **(B)** approach. **(A)** MSC cells are grown in the wells of cell culture plates and fluorescently (green) labelled magnetic nanoparticles (200nm diameter) are taken up by the MSCs. A single magnet on top of a cell culture plate acts as an external magnetic field, which levitates nanoparticle labelled cells, bringing them together to form a multicellular complex (spheroid). The spheroids can be transferred into a collagen gel, representing the architecture of the bone marrow, and used to test our candidate drugs.

(B) MSC cells are grown in tiny wells of a microfluidic device. The cells form spheroids because they cannot attach to the device. After spheroid formation, various BMP inhibitors were added to the spheroids and the spheroids were stained for viability (green=viable cells; red=dead cells; blue=nucleus of the cells where DNA is stored).

What did we find?

Preliminary experiments treating cells with our BMP inhibitors in combination with standard therapy have shown an increase in cell death of leukemic cells but not healthy cells. Treatment of only the MSC spheroids with our drugs did not impair growth or viability (see Figures 2 A and B), which confirms that our chosen inhibitors only target leukaemic cells. The collagen-based model allowed active migration of leukaemic cells towards the MSC spheroids embedded in a collagen gel (Figure 2C).

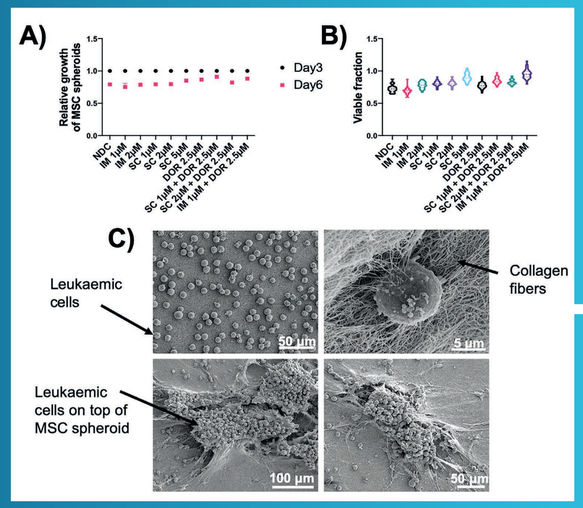

Figure 2(A) Growth and **(B)** survival analysis of MSC spheroids upon treatment with various drugs, including our BMP inhibitor called DOR, using microfluidics revealed no difference between the no-drug control (NDC) or drug (IM, SC and DOR) treatments. **(C)** Scanning electron microscopy imaging of leukaemic cells grown with MSC spheroids embedded in collagen revealed an active migration of leukaemia cells seeded on top of the collagen gels towards the spheroids.

What does this mean?

Our results show that targeting the BMP pathway might be a new and promising therapeutic strategy for leukaemia. Using microfluidic devices or our nanoparticle model enables us to study cell-cell interactions within a realistic setup, as well as new therapeutic approaches and the processes leukaemia cells undertake during disease progression. We hope this will help us identify other effective candidate anti-cancer drugs.

Who am I?

I am a final year PhD student at the University of Glasgow. I studied Biology back home in Germany with a focus on Molecular and Cell Biology during my Masters degree. After my PhD I would like to supervise clinical trials.

Caroline started her PhD project entitled *"Investigating leukaemic stem cell opportune remodelling of the bone marrow microenvironment"* in 2016 and while principally based at the University of Glasgow, supervised by Dr Catherine Berry and Dr Helen Wheadon, she is also working closely with Collagen Solutions Ltd.