ICR The Institute of Cancer Research

Final Update Report written by Stella Man, May 2025.

The investigation of markers associated with Epithelial to Mesenchymal Transition (EMT) to derive novel therapies for Desmoplastic Small Round Cell Tumours (DSRCT).

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Desmoplastic Small Round Cell Tumours (DSRCT) are a very rare and aggressive cancer that mostly affects young people between 10 to 30 years old. These tumours often start in the abdomen and because they don't cause clear symptoms at first, they're usually found late—when they've already spread. Current treatments include surgery, chemotherapy, and radiation, but they often don't work long-term. Sadly, fewer than 15 out of 100 people survive more than 5 years after diagnosis.

Thanks to your support, in 2022 we developed tiny 3D models of DSRCT in the lab (similar to mini tumours), to study how cancer cells interact with nearby helper cells. These helpers, more specifically known as cancer-associated fibroblasts (CAFs), can assist the tumour in growing and spreading. Using these models, we found signals and genes that may play key roles in this interaction. This allowed us to identify a drug that blocks the interaction and prevents tumours from progressing.

As a result of the interaction between the DSRCT cells and CAFs, a key process called Epithelial-Mesenchymal Transition (EMT) featured strongly in our analysis. This is when cancer cells change their shape and behaviour. Typically, cells act like bricks in a wall and will stay put and form protective barriers, whereas in EMT, they can escape by becoming more flexible and mobile which enables them to spread through the body. Both EMT and the reverse process, Mesenchymal-Epithelial Transition (MET), have previously been reported by other DSRCT researchers, and our findings support that.

This year, we focused on spotting the exact signals of EMT in tumour samples from patients. We used a powerful new microscope tool (the Phenocycler Fusion) that lets us stain and see many markers at once on a single tissue slice. Think of it like using color-coded highlighters to mark different parts of a map. To make this work:

- We used antibodies that fluoresce under the microscope when they find a certain marker.
- We tested these antibodies on tissues known to have or lack each marker, to make sure they work correctly.
- We obtained legal permission to use these samples through special agreements (Material Transfer Agreements) with two tissue banks based in Imperial College, London.

Besides EMT signals, we also looked at other markers (see Fig 1). These include:

- Blood vessel markers (ERG),
- Low-oxygen areas (hypoxia) markers (CAIX, GLUT1),
- Different types of CAFs (IL-8, αSMA).

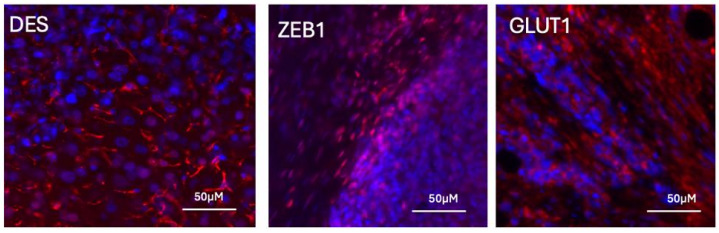

Fig. 1 Optimised markers in preparation for multiplexed Phenocycler analyses. Example images of tissue sections stained for markers Desmin (mesenchymal cells), ZEB1 (EMT) and GLUT1 (hypoxia) appear in red. The blue colour highlights where each cell is located in the tissue section.

To find the actual DSRCT cancer cells, we are now using a very recently discovered marker called CACNA2D2, which is linked to the abnormal fusion of two genes (EWSR1 and WT1) found in all DSRCT cases. This helps us find these cancer cells more easily.

We have also created live cell models with fluorescent tags to help us monitor how DSRCT cells behave in real time. These tags light up depending on which state the cell is in. We are interested in three specific cell states:

- Epithelial (less mobile),
- Mesenchymal (more mobile and aggressive),
- Neuronal (represent more primitive cells that are more likely to evade treatment).

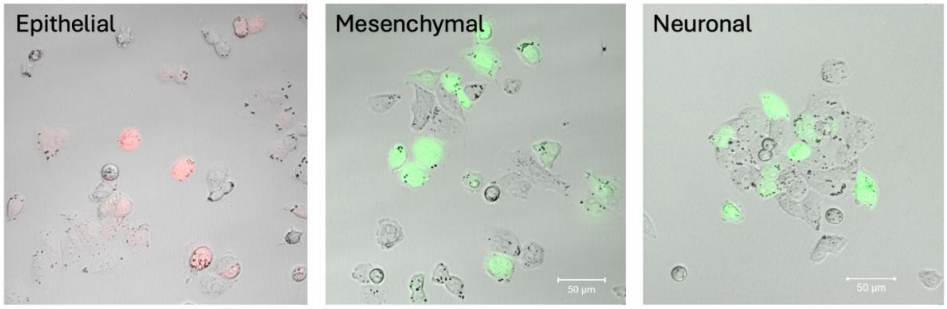

Fig. 2 Live DSRCT cells fluorescently tagged with markers in different states (Epithelial, Mesenchymal and Neuronal)

Each of these states could play different roles in how the tumour grows, spreads, or resists treatment. Eventually, we'll combine all three tags into one model. This will allow us to track single cancer cells as they switch between states—almost like watching a mood ring change colour. This gives us a powerful new way to see how different treatments affect cancer behaviour.

Next steps

Once we have found the optimal staining conditions for the final marker (CACNA2D2), we will stain tumour samples from 12 DSRCT patients with all the markers in our panel. These will be scanned using the Phenocycler system, giving us a detailed map of how different cell types are arranged within the tumour.

We will then compare the results from real patient samples with our lab-grown models. This will help us understand how the tumour's environment—like low oxygen or surrounding helper cells—influences how cancer cells change. We also hope to spot early signs of cells shifting between states, which could point to the best time to intervene with treatment.

Thank you very much once again for your generous support of our work.


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