Developing targeted treatments for DSRCT patients

Prepared for Rob's ARTTT by Professor Janet Shipley, Dr Ewa Aladowicz & Dr Stella Man (Sarcoma Molecular Pathology Group) in conjunction with Nicola Shaw (Development Office)

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Recent research progress

Professor Janet Shipley and her Sarcoma Molecular Pathology group at The Institute of Cancer Research have been supported by Rob's ARTTT for 15 years. Over that time, many exciting discoveries have been made particularly towards making better models to test potential treatments. Support from Rob's ARTTT has been key to making much of the progress possible. Recently Rob's ARTTT visited the group at their laboratories in Sutton to hear about the latest research advances.

Dr Ewa Aladowicz has been working to develop new laboratory models of DSRCT derived from patient samples. Despite growing so aggressively in patients, the cancer cells are notoriously challenging to grow successfully in the laboratory setting. The cancer models Ewa is working extremely hard to cultivate are incredibly valuable research resources as cases of DSRCT are rare.

Ewa is growing cancer models in 3D tumour-like spheres, rather than flat on the bottom of petri dishes. By doing so, the models more closely mimic how tumours appear and behave in the body.

A key feature of DSRCT is the presence of the EWS-WT1 fusion protein. This protein is the result of a 'fusion gene' – a hybrid gene formed from two previously separate genes. The fusion protein can bring about some of the particularly aggressive features of DSRCT – growth without limit, avoiding cell death, and spreading from its primary site. Models are being grown in the laboratory where this fusion protein is inserted into normal cells to study its role in sensitivity to drugs.

Ewa works on establishing models from different patients. By cultivating as many diverse models as possible, the fullest picture of disease diversity from patient to patient can be built. Potential treatments can be tested in these models, with drug combinations and dosing levels being fine-tuned to identify the most effective strategies. This can create an understanding of which patients would benefit from specific treatments and predict when resistance to treatment could arise.

Dr Stella Man is shedding more light on how non-cancerous cells interact with and support DSRCT cells. Tumours in the body aren't purely made from cancer cells. In the case of DSRCT, cancer associated fibroblasts (CAFs) are known to be in high numbers around cancer cells. These CAFs form tough, densely packed scar tissue around DSRCT preventing treatments from

reaching the cancer cells effectively. The scar tissue also supports the growth and the ability for cancer cells to spread around the body.

Stella has been creating co-culture models in the laboratory that have both DSRCT and CAF cells. These co-cultures are being used to test potential treatments. They also enable investigation of the ways the two types of cells interact with each other through signalling pathways that resist treatment and promote tumour spread. The group have already identified multiple signalling pathways of interest, including one known as the PDGF/PDGFR pathway. When active, it can promote cancer cell division, cancer cell spread, and promote the development of scar-like tissue formation. The team is currently testing an existing drug to target this pathway that is already in clinical use (though not previously used for DSRCT). The drug shows excellent promise in slowing cell division, killing DSRCT cells, and reducing cell spread.

There are many exciting next steps in this area. Firstly, the team will be speaking to clinicians in Europe to find out how this promising drug may be used in DSRCT patients. They will also be investigating other interesting signalling pathways they have identified to find suitable drugs to target them with. There will also be collaborations – both with colleagues at The Institute of Cancer Research to investigate suitable targets, and with researchers in other institutes in Italy and the Netherlands to share DSRCT models.

Another exciting avenue for Professor Shipley and the group is the development of a treatment strategy based on the activity of the fusion gene – which could be an Achilles heel to the cancer cells. In collaboration with another group, Professor Shipley's group has identified that the presence of this fusion protein puts pressure on how DNA is copied inside cells before every cell division. This pressure results in DNA damage that cancer cells need to repair. But if the team blocks this repair process with a new drug, excessive DNA damage can accumulate which kills DSRCT cells. This drug can also be combined with chemotherapy that increases the damage to DNA and potentially kill cells with lower doses - importantly reducing the damage to healthy cells.

The group has demonstrated these ideas using different models developed in the laboratory, including a DSCRT cell line and the models that Ewa has developed that can switch the fusion protein on and off.

All this work requires numerous experiments and the creation of large amounts of data that needs to be interpreted. The group has recently been able to utilise a new piece of equipment called the Opera Phenix high content imager microscope. This high-tech piece of kit has been a gamechanger for the group and other groups at ICR. It allows them to image multiple cancer models simultaneously in a fraction of the time it would have taken previously. The technology is being programmed to count different cell types in samples – something that the team have had to do manually in the past. The equipment has allowed them to gather more detailed knowledge and also streamline processes to reach conclusions sooner and move research forward faster.

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