Research to identify new Treatments for Desmoplastic Small Round Cell Tumours

Report prepared for Rob'sARTTT by Drs. Ewa Aladowicz, Antonio Romo-Morales and Stella Man, Professor Janet Shipley (Sarcoma Molecular Pathology Team) and Nicola Shaw (Development Office)

August 2022

Background

Desmoplastic Small Round Cell Tumour (DSRCT) is a particularly aggressive type of sarcoma that occurs mostly in adolescent and young people. It is very difficult to treat and has a poor prognosis. Due to its rarity, DSRCT is studied by very few scientific research groups. Current treatment for DSRCT involves standard surgery, chemotherapy and radiotherapy. These treatments may initially destroy cancer cells but are, unfortunately, rarely effective in curing patients as resistant cancer cells re-grow. Treatment also harms normal, healthy cells resulting in unwanted side-effects.

Progress in understanding the biology of both the cancer cells and cancer-associated normal cells that make up the 'desmoplasia' of DSRCT is behind that of other types of cancer. This lack of molecular understanding hinders the development of new therapies. To overcome these issues, it is important to develop models of DSRCT that can be used to investigate what specific molecular events drive the growth and progression of DSRCT and ways of targeting these.

Progress

New models

Ewa is continuing to make new models of sarcomas derived from patient's tumour samples. We have the necessary permissions to collect these samples from young patients with soft tissues sarcomas at Royal Marsden Hospital and Great Ormond Street Hospital. Currently these can only be grown in mice and Ewa is testing various media cocktails to try and grow these in our tissue culture area of the laboratory that you saw on your recent visit. This will expand the number of DSRCT models available to capture the diversity we see in patients. The aim is to then to characterise, further develop and use these models in our testing program of drug combinations.

The role of Dysplasia in DSRCT and testing a new treatment

Desmoplasia forms when cancer cells attract nearby non-cancerous cells, known as fibroblasts. These cells also occur after a small skin injury in order to heal the wound. In DSRCT this creates a tough physical barrier made of proteins around the tumour cells - supporting the growth and survival of the cancer cells. It also creates an obstruction that limits the effectiveness of treatments.

Stella has re-created the desmoplasia that surrounds and assists the growth and spread of DSRCT using two cell-types: cancer cells and cancer-supporting fibroblasts, in the form of 3D spheroids (Figure 1). This co-culture model of DSRCT has been used to test drugs that are already available in the clinic but not previously used for DSRCT. This will enable quicker potential to use in patients. A promising drug candidate that targets an important growth factor

in DSRCT has been identified and early results suggest that it is able to kill and stop cancer cells spreading. It is now being investigated in greater detail to find ways to further bolster these effects eg. by combining with standard chemotherapy drugs. Since the spheroids are live cultures, we can now monitor the functional behaviour of both cell types together using time-lapse imaging techniques. Our aim is to find new strategies to interrupt/interfere with the key communication processes between the different cell-types that drive disease progression.

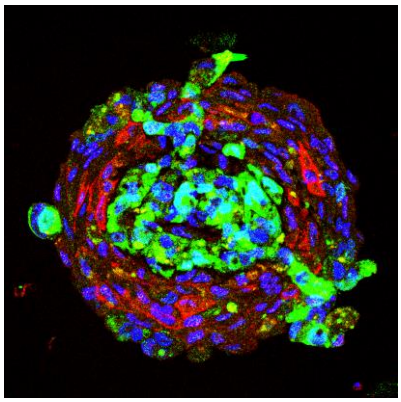

Figure 1: 3D co-culture model of DSRCT. *A microscopic image showing the cross section of a 3D spheroid consisting of DSRCT cancer cells (shown in green) and cancer-supporting fibroblasts (shown in red). The fibroblasts are arranged around the central core of cancer cells as similarly arranged in tumours from DSRCT patients.*

Treatment for DSRCT based on the EWS-WT1 fusion

Antonio is working on developing a new combination treatment for DSRCT patients. The aim of this treatment is to exploit of one of the key characteristics of DSRCT cells, the EWS-WT1 fusion protein. Our hypothesis is that 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 fix, but if we block this repair process with a new drug, excessive DNA damage can kill DSRCT cells (Figure 2). This drug can also be combined with chemotherapy (using existing drugs used to treat DSRCT) to increase the damage to DNA and potentially kill cells with lower doses - importantly reducing the toxicities to healthy cells. Overall, this strategy targets a weakness that is specific to DSRCT due to the presence of fusion protein EWS-WT1, making this type of treatment directly tailored to this sarcoma. Our next steps are to demonstrate these ideas using different models developed in the lab, including Stella's co-culture model containing cancer cells and fibroblasts and Ewa's patient derived models.

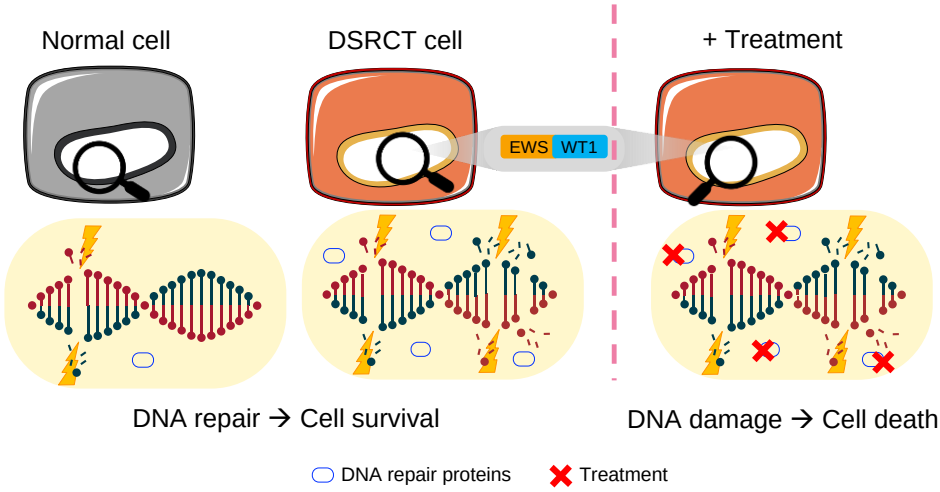

Figure 2. Targeted treatment against DSRCT cells. *The process of copying DNA in DSRCT cells is put under pressure by the characteristic fusion protein EWS-WT1. This stress*

creates DNA damage that needs to be repaired for cells to survive. Treating DSRCT cells with a drug that targets DNA repair proteins results in that damage not being repaired causing the cancer cells to die.

We collaborate closely with colleagues in the Children and Young People's Unit and Sarcoma Unit from Royal Marsden Hospital, the European paediatric Soft Tissue Sarcoma Study Group (EpSSG) and Innovative Therapies for Children with Cancer (ITCC) Consortium. These links will allow us to ultimately bring new therapy regimens into DSRCT patients sooner.

Thank you

We would like to thank Rob's ARTTT for their continuing and generous support. We hope you are proud to hear more about the progress you have helped to make possible. Your generosity has allowed us to purchase vital laboratory reagents which we simply could not undertake our research without. We look forward to updating you on further advances your tieless work will make a reality, in Rob's name and honour.