# Desmoplastic Small Round Cell Tumour (DSRCT):
## Discovering therapeutic targets to improve treatment for children and young adults with DSRCT

Update for Robs ARTTT
August 2013

A revolution is taking place in the way that cancer is treated. 'One size fits all' treatments are being abandoned in favour of precision targeting of tumours using individualised strategies based on a vastly increased understanding of the biology and genetics of cancer.

Development of new treatments for children's cancers has traditionally received less investment than adult cancers, particularly when it is rare disease such as DSRCT. However we are tirelessly working to ensure children and teenagers are getting the treatments they need and deserve.

Since 2010 Robs ARTTT have generously provided over £140,000 towards funding a researcher in Dr Janet Shipley's laboratory at The Institute of Cancer Research (ICR). This allowed Dr Shipley to extend her research on rhadomyosarcoma to include the very rare and aggressive Desmoplastic Small Round Cell Tumours (DSRCT). The aim of this research is to find new therapeutic targets which could potentially help to improve cure rates, reduce side effects and improve function and quality of life for young cancer patients.

The past 12 months have seen a change in personnel. Dr Barbara Villarejo Balcells, for whom this funding has been supporting, left the ICR in October 2012, to be replaced by Dr Ewa Aładowicz. However we are pleased to say, that to meet the vision of Rob Holland to fund DSRCT research in the UK, we are still making real progress.

Rob's mum, Amanda hands over a cheque to Dr Ewa Aładowicz, surrounded by Dr Janet Shipley, Dr Zoe Walters and Robs ARTTT Trustee Caroline Busby

## Background

Little is known about the underlying biology of childhood cancers. Children and teenagers still tend to be treated with un-specific and toxic chemotherapy drugs designed for adults. The side effects of these drugs can be devastating: growth abnormalities, cosmetic deformity, and secondary cancers and infertility in later life.

Soft tissue sarcomas are a group of tumours that arise in the soft supporting and connecting structures of the body, such as muscle and fat. The most common soft tissue sarcoma is rhabdomyosarcoma which resembles muscle and primarily affects children and young adults. In the UK, there are around 70 new cases of childhood rhabdomyosarcomas every year. Other soft tissue sarcomas occur less frequently, for example, there are around 3 new paediatric cases of DSRCT each year in the UK.

Certain types of rhabdomyosarcomas and DSRCTs are very aggressive with very poor survival rates despite the use of highly intensive therapy. Therefore, we need to find new ways to treat paediatric soft tissue sarcomas. In addition, we need these treatments to be safer for the growing child to prevent the long lasting developmental effects associated with such intensive treatments. To develop better and safer treatments we first need a thorough understanding of how these tumours work at the detailed molecular level.

RobsARTTT has been kindly supporting the work of Dr Janet Shipley and her team at the ICR to understand the biology of soft tissue sarcomas, including rhabdomyosarcomas and DSRCTs.

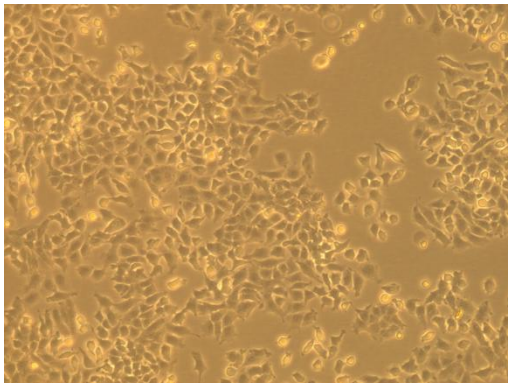
Our work focuses on understanding the molecular biology of these tumours (how the structures within normal cells and tumour cells work) so that we can find new ways to classify patients and identify new avenues of treatment that will improve the clinical management of these patients.

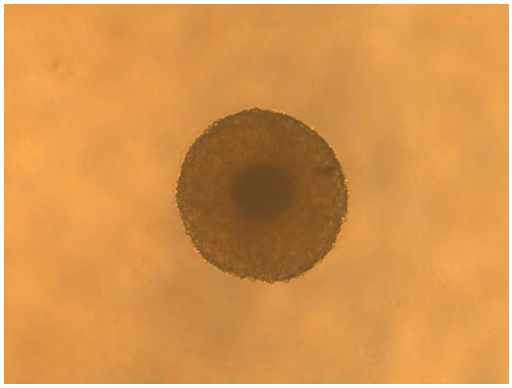
## DSRCT progress

Written in conjunction with Dr Janet Shipley and Dr Ewa Aładowicz

Our cells contain lots of genes that help control how the cells behave. To understand more about how genes are controlling DSRCT cells, we have grown DSRCT cells in the laboratory and conducted a gene expression profiling experiment on them. This involves investigating the genetic information from DSRCT cells and doing experiments to see which genes are active or inactive in these cells. Highly active genes are likely to play a role in DSRCTs and these genes could be targets of attack for future new therapies.

Traditionally these new therapies in the form of drug compounds, are tested on two dimensional cell lines (pictured left), however can lead to failure of drugs in clinical trials as the tumour behaves differently in this form compared to how it would in the body. We have now developed three dimensional models of DSRCT (pictured right) which more accurately represent how tumour cells behave and will therefore provide a better model to assess whether a drug is likely to be successful in the clinic.





Last year we reported how we obtained our first DSRCT cell line and we are pleased to say we are now collaborating with other groups to get more newly established cell lines. This is important to represent as much biological diversity among patients as possible, as not all tumours of same type of cancer are identical and can contain different genetic mutations.

We have found 77 genes that could be important in DSRCT. After blocking the activity of these genes we have come up with a list of potential druggable targets for this disease. Importantly we have also identified 3 genes in particular for which there are already drugs in clinical trials for other cancer types. This is very exciting as it will be quicker to test a drug for use in DSRCT cases if it has been approved for use in other cancers already, particularly important in a rare tumour type where the number of cases is too low to run a full clinical trial.

Our studies on DSRCT also include genes that are associated with histone modifying enzymes. Histone modifying enzymes are involved in turning other genes on (active) or off (inactive), which is a normal process in all cells but may be abnormal in tumour cells.

Our work with rhabdomyosarcoma tumour cells showed that these cells are addicted to high levels of certain histone modifying enzymes and that reducing their levels, reduced the ability of rhabdomyosarcoma cells to grow. We have now investigated whether DSRCTs are also addicted to histone modifying enzymes. Our results indicate that there are a number of histone modifying enzymes that are important for DSRCT growth. We are now examining these more closely and working on them in conjunction with the Division of Cancer Therapeutics at the ICR as part of a larger study.

Our work on histone modifying enzymes appears very promising. Our close working relationship with the Division of Cancer Therapeutics at the ICR and the links with the Royal Marsden Hospital as well as national and European organisations enables us to be at the forefront of sarcoma research with potential to move discoveries forward to benefit patients with rhabdomyosarcomas and DSRCT.


Rob’s friend Thomas has a go at pipetting in the laboratory

## About The Institute of Cancer Research

The Institute of Cancer Research, London is one of the world's most influential cancer research institutes. Our mission is to make the discoveries that defeat cancer.

Scientists and clinicians are working every day in our labs to make a real impact on cancer patients' lives. Through our unique partnership with The Royal Marsden Hospital and 'bench-to-bedside' approach, The Institute of Cancer Research (ICR) is able to create and deliver results in a way that other institutions cannot. Together, the two organisations are rated in the top four cancer centres globally.

The ICR has an outstanding record of achievement dating back more than 100 years. We provided the first convincing evidence that DNA damage is the basic cause of cancer, laying the foundation for the now universally accepted idea that cancer is a genetic disease. Today we lead the world at isolating cancer-related genes and discovering new targeted drugs for personalised cancer treatment.

As a college of the University of London, the ICR provides postgraduate higher education of international distinction. We have charitable status and rely on support from partner organisations, charities and philanthropists.

**Making the discoveries that defeat cancer**

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