The Institute of Cancer Research: Royal Cancer Hospital

Registered Office: 123 Old Brompton Road, London, SW7 3RP
tel: 020 7352 8133 | fax: 020 7370 5261
web: www.icr.ac.uk

Year 2 Progress report for RobsARTTT

Funding a researcher to study DSRCT

In 2010 RobsARTTT generously agreed to provide funding to The Institute of Cancer Research (ICR) towards a researcher in Dr Janet Shipley's laboratory for 3 years. 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.

Ahead of our meeting at the end of year 2 of this project, we provide a short update for you on the progress made over the past 12 months. This has been written in conjunction with Dr Janet Shipley and Dr Barbara Villarejo Balcells, for whose position the RobsARTTT funding allowed us to recruit and support.

June 2012

Background

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 Desmoplastic Small Round Cell tumours (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.

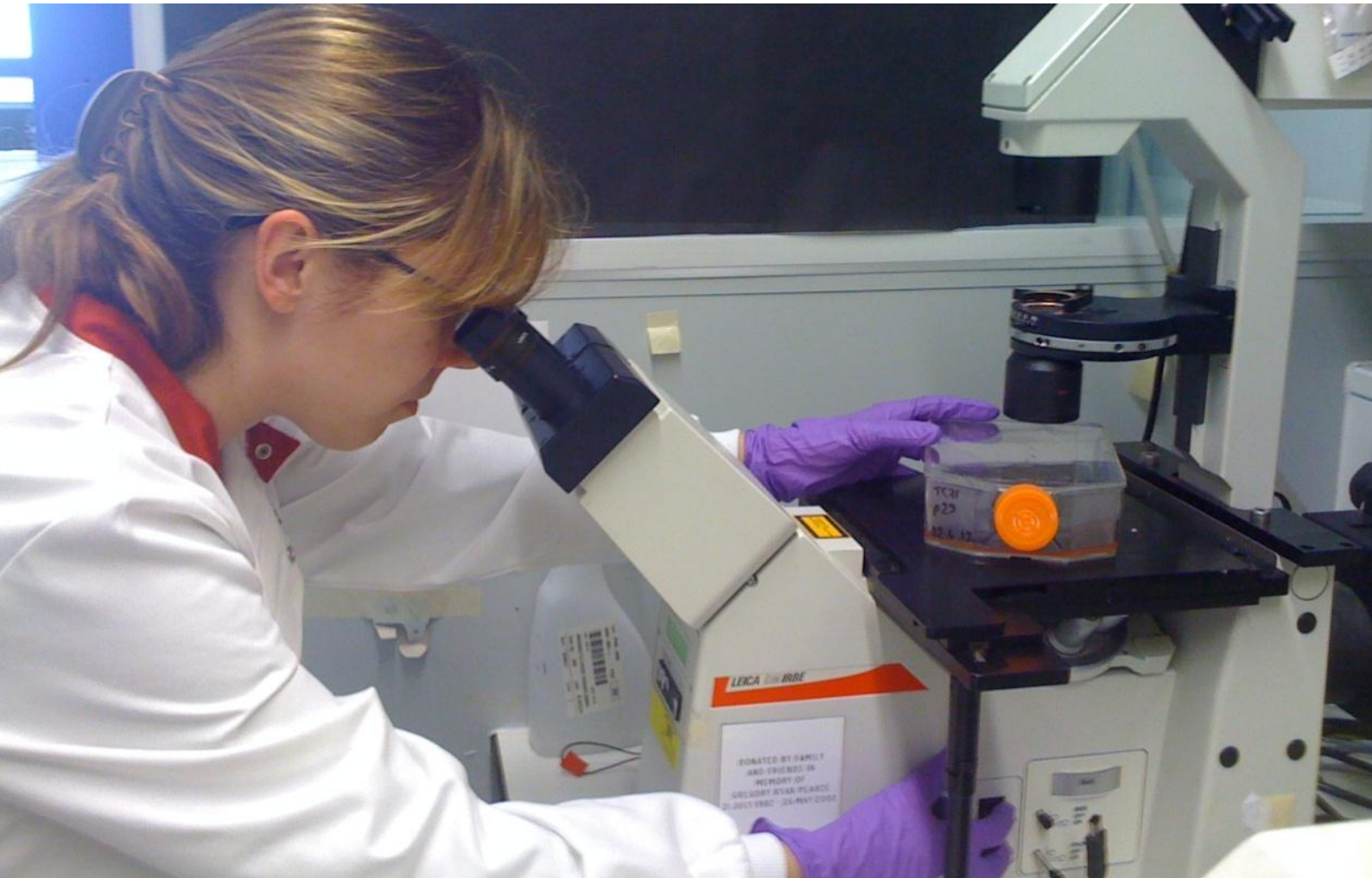
RobsARTTT has been kindly supporting the work of Dr Janet Shipley and her team at The Institute of Cancer Research (ICR) to understand the biology of soft tissue sarcomas, including rhabdomyosarcomas and DSRCTs. Our work focuses on understanding the molecular biology (how the structures within normal cells and tumour cells work) of these tumours 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. This is exemplified by our recent published study that identified a new way to classify rhabdomyosarcoma patients into various groups according to their risk of having more aggressive cancer and not responding well to standard treatment (study published in The Journal of Clinical Oncology in March 2012 and outlined later in this report). By grouping patients we could tailor their treatment accordingly, with low-risk patients avoiding the side-effects of intense treatment while high-risk patients could benefit from more intense treatment.

DSRCT progress

In our previous update to RobsARTTT, we presented our progress in identifying important molecules known as histone modifying enzymes as potential new targets for rhabdomyosarcoma treatment. We also presented our efforts in obtaining DSRCT cells and our plans to extend the rhabdomyosarcoma research to DSRCTs. In this update, we would like to present our progress on the DSRCT work that we have conducted.

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. Having this information available is crucial for our current work on DSRCT and also for future work because it tells us whether a particular gene is likely to be important in these tumours. Highly active genes are likely to play a role in DSRCTs and these genes could be targets of attack for future new therapies. We have now concluded the gene expression profiling and have this important information available for reference.

Dr Barbara Villarejo Balcells in the lab



We have also extended our studies on histone modifying enzymes to DSRCTs. Histone modifying enzymes are involved in turning 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 (see below for further information on the Division of Cancer Therapeutics).

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.

Unique environment

The Institute of Cancer Research (ICR) has the largest academic drug discovery unit in the world, the award winning Cancer Therapeutics Unit, which has discovered 16 innovative drug candidates over the past six years, with the progression of six of these drugs into Phase I clinical trials: a feat unmatched anywhere else in the world. Unique to academic centres worldwide, the ICR has an on-site medicinal chemistry unit, with the capability to invent and chemically synthesise (produce) cancer drugs, in collaboration with biological scientists and medical doctors. It is very uncommon that a single centre possesses all the combined expertise to move from concept through the laboratory and into the cancer clinic. The ICR has discovered many drugs that are now used worldwide, for example, melphalan, busulfan and carboplatin. Most recently abiraterone has been discovered, which has been a major landmark drug for prostate cancer. We are now working to discover new drugs for soft tissue sarcomas such as rhabdomyosarcoma and DSCRT.

Test for single genetic fault can predict child cancer patient survival

Taken from a press release, 26th March 2012
A study led by the ICR has shown that a simple genetic test could help predict the aggressiveness of rhabdomyosarcomas in children and should be introduced into clinical practice. The test would lead to changes in treatment for many patients, allowing some children to escape potentially long-term side-effects whilst giving others the intense treatments they need to increase their chances of survival.

In a paper published online in the Journal of Clinical Oncology, Dr Janet Shipley and collaborators in the UK, Switzerland and France found that children who have a tumour called rhabdomyosarcoma with a particular genetic fault (a fusion gene) have significantly poorer survival rates than other rhabdomyosarcoma patients.

Children diagnosed with rhabdomyosarcoma are treated with a combination of chemotherapy and surgery and sometimes radiotherapy. These treatments have helped improve survival rates, but can cause serious and long-term side-effects including the potential to develop another cancer later in life. Having better information about how aggressively the tumour is likely to behave can help doctors to tailor treatment for each patient that balances the need for effective treatment with the side-effects of such treatment.

Dr Shipley says: “Our previous studies have raised issues with the current system of predicting patients’ risk, which is based on the appearance of patients’ tumours. Our new study finds that a simple genetic test should be incorporated into standard clinical practice as it significantly improves our ability to predict tumour aggressiveness. This fusion gene test could be used alongside other standard clinical measures to divide patients into one of four risk-groups, so that treatment can be tailored accordingly. Importantly, this will mean some patients who were previously categorised as high-risk could be able to avoid the side-effects associated with intense treatment, while others should receive the intense treatment they need to increase their chance of survival.”

In this study, which was partly funded by the Chris Lucas Trust – a funder set up in similar tragic circumstances to RobsARTTT - Dr Shipley’s team analysed data for thousands of genes from 225 rhabdomyosarcoma samples. This identified a panel of 15 gene alterations that could be used to predict how patients responded to treatment. However, these gene changes were mostly linked to the presence of the particular fusion gene, which is much simpler and cheaper to test for than the other alterations. The test would involve scanning for the presence of the fusion gene in a sample of the patient’s tumour.

Combining the fusion gene test with two existing standard measures of risk for rhabdomyosarcomas – the patient’s age at diagnosis and the tumour’s stage of development – gave a simple but highly effective prognostic test.

Lynn Lucas, whose son passed away in July 2000 after a three year battle with rhabdomyosarcoma, says the Chris Lucas Trust helped fund the team’s important research in the hope that other children and parents would be spared their ordeal. Treatments for the cancer left Chris with serious side-effects including weight loss, difficulty walking and a painful mouth.

“Rhabdomyosarcoma is a cruel disease since children can go into remission thinking they have won the battle then find out months later it has returned even more aggressive,” she says. “The current treatments have some dreadful side-effects, which children have no choice at present but to tolerate. This test could help some children avoid this suffering, making sure only those who really need it receive intense treatment.”

The study was a collaboration between the ICR, The Royal Marsden NHS Foundation Trust, the Northern Institute for Cancer Research and University College London Institute of Child Health in the UK; SIB Swiss Institute of Bioinformatics and the Centre Hospitalier Universitaire Vaudois in Switzerland, and the Institut Curie, Ligue Nationale Contre le Cancer and Institut Gustave Roussy in France.

We remain extremely grateful to RobsARTTT for the total pledge of £100,000 towards funding Dr Villarejo’s role over 3 years as we aim to make the advances necessary to meet Rob’s vision to help others affected by this devastating cancer.

Thomas Bland – Deputy Director of Development (Trusts & Corporates)
E: thomas.bland@icr.ac.uk, Tel: +44 (0) 20 8722 4200, W: www.icr.ac.uk