



Where does your money go?

All profits raised by William's Fund go directly to Dr Chris Mitchell at the Oxford Radcliffe Hospital for research into childhood cancers. There are no administration fees and no paid employees at William's Fund. Please read on for an update on the research project from Dr Mitchell.

Research Update from Dr Chris Mitchell (August 2005)

It has been some time since we updated the report on the website, and there has, of course, been progress with our work over the past months. We now have two projects, the first and original one which is looking at some of the underlying genetic abnormalities in childhood connective tissue tumours, and the second, and much smaller project, which is examining similar mechanisms in childhood leukaemia.

We have made a lot of progress with the main project over the past months, following a lot of hard work and a number of setbacks. However, we have now reached a point where we can hope for substantial progress over the next few months as we analyse our new results and design new experiments to answer the questions that are now raised. It is a continuing process, and we remain a long way from understanding the "cause" of this kind of cancer.

The leukaemia project has already given some interesting insights into the underlying genetic mechanisms. This work is very much at a preliminary stage, but we hope to develop this project further over the next few years.

Project 1: Genetic mechanisms in childhood sarcomas; (personnel: Sophie Hill, PhD and Elizabeth Rapa MSc)

Sophie Hill, who started working with us in March 2001, has continued to work part time in the laboratory since the birth of her second son. Elizabeth Rapa, who started work for us in March 2002 brought a great deal of experience in the molecular biology of cancer and has been a great addition to the team. She is now registered at Wolfson College, the University of Oxford for a Doctorate in Philosophy. Both Elizabeth and Sophie are working on a tumour called rhabdomyosarcoma, which is a type of cancer that develops in muscle cells and is seen mainly in children. Emily Carpenter continues to work intermittently in the lab, fitting this work around her medical studies and has concentrated on the genetic abnormalities that underlie the development of leukaemia.

These three appointments have been possible only as a result of the generosity of the friends and family of William Dodd. We are grateful to Peter and Johanna Dodd for this opportunity to thank all of you who have given so generously to support this research. The past year has at times been very frustrating in the lab, but now we have a lot of new information, which is at last enabling us to design new experiments that should yield some exciting answers about the underlying causes of this type of cancer.

First, we need to explain a bit about genetics. Everything about us is encoded in the chemical known as DNA. The DNA in our cells is organised into genes and the genes in turn are organised in chromosomes. The genes provide the blueprint for producing all the proteins that cells need to function. A human cell contains about 100,000 genes, organised into 23 pairs of chromosomes. In any one cell though, only a few genes relevant to that cell's function are turned on or "expressed". Obviously, it is important that the DNA is kept in proper condition while the cells do the work required of them or when they divide, so there are intricate mechanisms within the cell to make sure that any damage is properly repaired and that the chromosomes replicate themselves properly. These mechanisms are also encoded in the genes, so it is rather like having a car that can repair itself if it stops working properly, or can make itself a new one when the old one wears out!

Occasionally, however, when a cell is damaged or divides, the processes do not work properly and the chromosomes can get jumbled up - a process called chromosome translocation. For example, a bit of chromosome 2 can break off and get stuck onto a broken bit of chromosome 13. When this happens part of a gene on one chromosome adjacent to the break can find itself in the company of part of another gene adjacent to the break on the other chromosome. The two genes can then get spliced together to make a completely new gene with all sorts of unusual properties.

Many malignant tumours have within their cells recognisable and specific rearrangements of their chromosomes, and often it is possible to demonstrate that the affected genes have combined to make either a new protein or one that expressed when it shouldn't be. We are particularly interested in a translocation between chromosomes 2 and 13 seen in rhabdomyosarcoma. We think that the translocation results in one or more genes being turned on or off inappropriately. We are trying to understand how it is that such abnormalities of genetic control can happen, in the hope that we might in due course discover ways of re-establishing normal control. Such a discovery might in due course provide us with a completely new way of treating this type of tumour, and might also give us hints for dealing with other types of tumours.

With the support of William's Fund, we have worked to identify genes that are no longer regulated properly, presumably as a result of the chromosome translocation that we described above. The technique - called "representational difference analysis" - was difficult to master and prone to not working - usually for no very obvious or good reason. At last, the technique has been optimised and we have now completed a number of experiments, leading to the identification of a number of genes that are not regulated normally in rhabdomyosarcoma. We chose eight genes to study further, based on features such as involvement in other types of cancer or because they are known to have roles in normal cell division. We have now confirmed that the regulation of these eight genes is significantly different in our cancer cells compared to normal cells. The next steps will include experiments, for example, to show what happens when a gene that that is over-expressed in a cancer cell is "turned off", and similarly what happens when a gene which is under-expressed is turned "back on". This work is the basis of a thesis that Elizabeth is submitting for a Doctorate in Philosophy.

We are also continuing to work on disentangling the series of events in cells at different points during cell of division - called the cell cycle - so as to identify genes that are inappropriately turned on or off during this process. This series of experiments involves sorting the cells into different populations according to their stage of division. Then the cell messages (RNA) are allowed to "stick" to a "chip" which has sequences from thousands of genes embedded on its surface. Where the cell message finds its partner, it will stick and we can identify it. This method - which is fairly new - generates a great deal of data very quickly, and hence enables us to quickly plan more experiments for the future.

We are building up a complete picture of all the events that are going wrong in the cancer cell, but we still have a long way to go. We are preparing another grant application and are hopeful, after some encouraging comments from our last application, that this time we will be successful. As always, we are very aware that these grants are relatively small in number and extremely competitive. We remain extremely grateful to all of the supporters of William's Fund for giving us the opportunity to pursue our research.

Project 2. GATA1 mutations in childhood leukaemia. (Emily Carpenter BSc, Research Assistant (Temporary) supported by William's Fund)

I am a graduate entry medical student at Oxford University. Before deciding to embark on a career in medicine, I previously did a degree in biology. I am particularly interested in understanding the biology of cancer and how new-targeted therapies might improve the treatment of people with cancer. I have been very fortunate to receive support from William's Fund for some research work that I have been doing during my medical training.

I have been working with Dr. Chris Mitchell and Dr. Paresh Vyas at the John Radcliffe Hospital. Our work has focussed on improving our understanding of how acquired changes (mutations) in a particular gene (GATA-1), are involved in causing leukaemia in children. It is an important area of research because many advances have been made recently in our understanding of the biology of leukaemia, and these advances have the potential to make significant contributions to our knowledge of the general mechanisms of cancer formation.

To date I have been involved in work that has led to the publication of two research papers. This work was on looking for mutations in the GATA-1 gene in two children that had acquired three copies of chromosome 21 (trisomy 21) in their leukaemic cells. Normally each cell has only 2 copies of each chromosome (one from each parent), which carry genes encoded in DNA. This area was particularly interesting to study because the type of leukaemia the children had is called AMKL, which occurs at high frequency in children with Down syndrome. Down syndrome is known to be caused by the presence of trisomy 21 (i.e. three copies of chromosome 21) in all the cells of the body. However, it was unclear what role the trisomy 21 was playing in causing the leukaemia. Our work confirmed the presence of GATA-1 mutations in these two children with AMKL and trisomy 21 only in their leukaemic cells. This finding suggests that trisomy 21 plays a role in the development of leukaemia through its presence in the precancerous blood cells, rather than other cell types in the body.

This summer I have also been involved in a study looking for the presence of GATA-1 mutations in older children with Down syndrome. This work is very relevant area because a new chemotherapy trial is being carried out using lower doses of drugs in patients who have a GATA-1 mutation. The trial is being carried out because these children have much better chance of cure and respond better to lower drug doses than patients without the mutation. This work should lead to the publication of another paper in the near future.

I would like to thank William's Fund very much for the support I have received, without which I would not have been able to carry out this work. I really enjoy the opportunity to be able to do some research alongside my medical degree. I hope the experience this gives me means I will be able to continue to contribute to the field of research into children's cancers after I qualify as a doctor.

You can see this report and a lot more information and pictures on www.williamsfund.co.uk. Or call Johanna on 01753 899234