North of England Cancer Research Campaign

NEWSLETTER

ISSUE 6 | SUMMER 1997

Please don't forget to buy your Elephant! was our appeal to all customers of the Northern Rock Building Society throughout the whole of May. And they remembered in their hundreds - even thousands. At the last reckoning, nearly 4,500 NECRC elephant badges had been sold. In fact, they sold out so quickly we had to re-order more stock.

Our very grateful thanks to all the branches of Northern Rock in the region - 68 branches participated and made this a very successful fundraising event.

Thanks, particularly, to Libby Ellis-Clark at Northern Rock who master-minded it all.

We all know about the excellent quality of the research produced by our scientists which is regularly published in medical journals, but articles that start: "*The nuclear eukaryotic enzyme poly(ADP-ribose) polymerase [PARP (EC 2.4.2.30)] catalyses the transfer of the ADP-ribose moiety of nicotinamide adenine dinucleotide (NAD+) to nuclear acceptor proteins, in response to DNA strand-break formation...*" don't mean much to the average man (person!) in the street. Nor, in fairness, are they written for the general public. However, there's not much doubt that volunteers would welcome a "layman's guide" to such publications which is why we were so delighted when Samina Hamilton contacted the NECRC. Read her first two articles in this issue of the Newsletter.

Getting the Scientific Message Across

The aim of this Newsletter has always been to improve communications within the Campaign.

The first few issues concentrated on highlighting the excellent fundraising carried out by the Committees and illustrated various events. Later issues showed the wealth of good feeling felt towards the Campaign by members of the public who, quite spontaneously, raised large sums of money by organising various events.

However, it was always intended that an essential part of the Newsletter would be to explain the work of the scientists in such a way that it was clearly understood by lay members of the Campaign and the general public. Each issue has, therefore, included a list of the grants approved for the quarter and a brief summary of the purpose of each application.

In addition to the work currently being undertaken by the research staff, many papers are published each year in scientific journals which, in the format in which they are published, would clearly *not* be understood by anyone other than researchers who have an active interest in the subject.

NECRC was approached by Samina Hamilton, a scientist eager to "spread the word" to lay members of the public. Sam is eminently qualified for the job. Having completed her scientific training at Newcastle University, she followed her PhD in gastrointestinal physiology with a two year post-doctoral research project in viral infection in lung and heart-lung transplant recipients which she completed in 1994.

Since then she's been working in clinical research in the pharmaceutical industry.

However, she admits that during the past two and a half years, her activities in science writing and her Public Understanding of Science work have brought her great pleasure and satisfaction and she's eager to pursue these activities further. She has already written articles for other charities including the Talking Magazine for the Blind, the Transplant Support Network and the British Society for Immunology and is keen to help us.

With Mr Ross's approval, Sam was given selected papers and the two articles she produced are printed in this Newsletter.

More are planned for the future and I hope that ultimately we will have a copy of every article which is published by those scientists funded by the NECRC. In that way, volunteers will be kept informed of the up-to-date research and will have more information when invited to give talks or attend cheque presentation ceremonies.

Before being published in the Newsletter, or being used for any other publicity purposes, each article will be checked by the author and by Mr Ross to ensure that the research is being accurately presented.

From our coffers to the research institutions - exactly what happens to the money?

Scientists and doctors make the best use of donated funds

In 1995 the NECRC raised just under one and a half million pounds to fund medical and scientific cancer research. The money has always been put to good use and the past couple of years are no exception. Research into the treatment of a variety of cancers has been taking place at Newcastle upon Tyne's Medical School and Newcastle General Hospital (NGH), courtesy of the NECRC. Scientists and doctors at both institutions have singled out metastatic breast cancer, epithelial ovarian cancer and neuroblastoma as targets for their research activities.

Why the need for both lab and hospital-based research?

The link between scientific laboratory-based research and research done on real cancer patients is a crucial one which must be maintained so as not to let either form of research become too far removed from the other. Much lab-based cancer research is done on specially grown or cultured cancer cells taken originally from patients, but maintained over long periods in the lab. These cultured cancer cells are an ideal way to study what is taking place in cancerous cells without adding to the distress of the patient by taking blood or tissue from them on a regular basis. However, the hospital-based research on patients is also necessary because, once a possible treatment has been developed, it must be tested on real patients so that doses can be tailored to achieve maximum effect with minimum side-effects.

Genetics: what is it and why is it so vital to cancer research?

Study of the genes, or genetics, is a vital part of cancer research. This is best explained by some basic genetic principles. We inherit our characteristics from our parents as a set of "genetic commands" or chromosomes from each of them. 23 pairs of chromosomes exist in all our body cells, and they are essentially long strands of genetic material called DNA. The DNA is made up of many smaller elements called genes. Our genes determine all our characteristics, for example, eye and hair colour. Genes can be damaged in a variety of different ways and by numerous agents, or triggers, for example, radiation and poisons in the environment. These and other unknown triggers can start the development of different types of cancers: a damaged gene or piece of DNA may cause a wrong command to be given to a cell resulting in an uncontrolled dividing of that cell. This unchecked cell division results in cancer. By understanding that cancer has a basis in our genes, it is logical to target research at the gene level. This is achieved in the lab by studying genes in the cultured cells described.

North East researchers are constantly developing new treatments for:

1. Metastatic breast cancer

Research at NGH, headed by Professor Hilary Calvert, was conducted into metastatic breast cancer in 1995. This type of cancer spreads from the breast to other parts of the body and accounts for 12,000 deaths per year in England and Wales. At present, this form of breast cancer is incurable so treatment to relieve the symptoms (but not cure the illness) could improve the quality of the patient's remaining life. With this in mind, a new treatment regime was tested on women with advanced or metastatic breast cancer. Ifosfamide is a widely used chemotherapy drug which reduces the uncontrolled cell division which results in cancer. Epirubicin is equally widely used and is a cell-killing antibiotic. Therefore, together, these two drugs have a powerful effect on reducing cancer cell growth. Professor Calvert's research team had previously treated patients in 1990 with these drugs and had obtained promising results. However, they wanted to improve the effects of the drugs by using a naturally occurring substance in the body, called G-CSF, as a vehicle to deliver the drugs in higher doses and more effectively to the right place. In theory, this would also mean shorter periods of treatment for the patients due to increased efficiency of the drugs. In patient trials, this new combined treatment was shown to be as effective as other breast cancer chemotherapies, but specific advant-ages are reduced side effects and a much shorter course of treatment than for other chemotherapies. This treatment regime is still being developed for use in other types of cancers.

2. Epithelial ovarian cancer

Carboplatin is a platinum-based anti-cancer drug. Platinum agents are the most active single drugs for the treatment of advanced epithelial ovarian cancer, the biggest killer of all the gynaecological cancers in England and Wales. Professor Calvert's group at NGH again used G-CSF to deliver the carboplatin in higher doses and more effectively to the right place in women with this type of cancer. The team were able to effectively double the usual dose of carboplatin and side effects were minimal. The five year overall survival rate for this type of cancer sufferer is less than 38%. With this treatment in the patient group studied, so far, the three year survival rate is 52%. The treatment is currently being further developed.

3. A general anti-cancer treatment

There are many substances and stages involved in the making or synthesis of DNA. The uncontrolled dividing of cells, which produces cancer, depends on DNA being made at a rapid rate in an unchecked manner. If DNA synthesis can be interrupted at some point, then the resulting uncontrolled cell growth and the spread of cancer should slow down.

TS is just one substance required in the complex process of making DNA. There are several drugs available which interfere with TS's action and therefore can potentially stop DNA synthesis and hence growth of cancers. However, some cancers fail to respond or are resistant to these drugs and this is an escalating problem in the search for effective anti-cancer agents. Professor Herbie Newell's research group, based at the Medical School, worked with Professor Calvert's group at NGH to overcome the problem. Prof. Newell's group have hit on a drug called AG337 which interfere's with TS's action, but does not have the resistance problems of other drugs like it. AG337 was given to patients at NGH for whom other treatments had failed or where no other treatment was available. Samples of their blood were then tested (indirectly) for TS levels. If AG337 was having the desired effect, then TS levels in the blood would drop during treatment. This effect was seen but was not sustained after treatment ended. This promising preliminary research is continuing in the hope that treatment with AG337 can be developed to have greater long term benefit for cancer patients.

4. Neuoblastoma: Investigations at the laboratory stage

Research groups based in the Medical School headed by Christopher Redfern have been investigating the effects of two types of retinoic acid on neuroblastoma cells. Neuroblastoma is a cancer of cells which would normally develop into nerve tissue, but the process of development or differentiation into nerves has stopped. This type of cancer is mainly found in the adrenal glands of children under the age of four years. Retinoic acid triggers neuroblastoma to differentiate into nerve cells and is therefore seen as a possible treatment for this type of cancer. Dr Redfern's group cultured or grew neuroblastoma cells in the lab with two types of reinoic acid and then examined the cells under the microscope to see if the desired effect had been achieved, i.e. if they had differentiated to have nerves sprouting out of them. Both types of acid produced the desired effect, but one of the acids (called 9-*cis* retinoic acid) was more effective than the other. The added bonus of growing cells with the 9-*cis* acid was that the cells "committed suicide" once the acid was removed. This cell death (which makes way for new cells) combined with differentiation into nerve cells are both essential processes required for neuroblastoma cancer to shrink. This means that 9-*cis* retinoic acid may be a suitable treatment, if given intermittently for neuroblastoma. The next stage of this lab research would be to develop the treatment for use in patients.

Three way link is the way forward for cancer research

The triangle of co-operation between the NECRC, scientists and medics in our region has already yielded potentially important breakthroughs in the treatment of metastatic breast cancer, epithelial ovarian cancer and neuroblastoma in the past two years alone. The NECRC's continued funding of these vital research areas can only be for the mutual benefit of science as a whole and the cancer sufferers it aims to serve.

Laboratory-based cancer research: where new anti-cancer drugs start out

Inter-departmental co-operation in NECRC funded groups

Collaborative research projects between Prof Bernard Golding's group in Newcastle University's chemistry department, Herbie Newell's group in the Medical School and Hilary Calvert's group at Newcastle General Hospital has spawned some exciting developments in the area of new anti-cancer drugs from 1994 to the current date.

The menace of drug-resistant cancers

Investigations on new drugs by the chemists have focused upon the way that cancer spreads as cells multiply out of control. All our cells contain "genetic commands" in the form of long strands of DNA inherited from our parents. The DNA is made up of smaller elements called genes which makes us into individuals. Genes determine all our characteristics including our eye and hair colour. On occasion, genes (and therefore DNA) may become damaged. The damaged DNA may cause cells to multiply uncontrollably, causing cancer. There are many substances and stages involved in the making (or synthesis) of DNA. If DNA synthesis can be interrupted at some point, then the resulting uncontrolled cell growth and the spread of cancer should slow down. Many currently available chemotherapies or anti-cancer drugs work by interrupting the synthesis of cancer DNA. DNA, however, is a complex substance which has evolved ways in which to block the effects of many anti-cancer drugs. One method DNA uses is to repair itself once the anti-cancer drug has done the required job of damaging it. This special mechanism which is built into some types of cancer DNA means that some cancers may be drug-resistant.

Chemists lead the way in improving the effectiveness of existing anti-cancer drugs

The implications of this are serious for cancer sufferers, and with this in mind, Prof. Golding's chemists set about finding out how to exploit this resistance mechanism. They worked on a new generation of drugs called PADPRPs. They tested the function of several of these drugs by giving cancer cells grown up in the lab a dose of an anti-cancer drug called temozolomide, which damages cancer DNA. However, the cancer DNA is then able to repair itself and this reduces the effect of the temozolomide. The chemists found that by adding their new PADPRPs to the cancer cells and temozolomide, they were able to make the temozolomide more efficient at its job, by stopping the cancer DNA from repairing itself. This improved the effectiveness of temozolomide to such an extent that theoretically, the dose of temozolomide could be much reduced in patients if given with a PADPRP to improve its effect.

The research did not stop here though. PADPRPs were only effective in improving the action of a small number of anti-cancer drugs because of the way in which they acted upon the DNA. Still convinced of the potential of this type of drug, however, the chemists continued to study drugs which prevented damaged DNA from repairing itself. This time, they hit upon one called Wortmannin. Wortmannin was effective on a much broader range of anti-cancer drugs than the PADPRPs because it worked upon the DNA in a different way. This research at the laboratory stage is an exciting start to the search for drugs which can improve the effectiveness of existing major anti-cancer drugs by overcoming cancer's resistance to those drugs.

Geneticists exploit the function of DNA to limit the spread of cancers

Dr John Lunec's research group based in the Medical School has studied a substance called cathepsin L which is produced in large quantities around the site of new tumours. Reasoning dictates that if production of this substance by tumours could be limited, then the spread of cancers could also be limited. The group used cancer cells grown up in the lab to produce the cathepsin L. They were then able to work out the structure of the gene which produced it and several other related substances. The potential for suppressing the production of cathepin L and limiting the spread of tumours now exists because of this work.

Dr Lunec's group also recently studied the gene p53 which is known to suppress or stop the formation of tumours. PhD student Iakovos Sigalas has found a group of related substances produced by a range of human cancers, which inactivate p53 and hence

induce tumour formation. These substances work in a variety of hitherto undiscovered ways. This type of genetic research is frequently the forerunner to developing new ways to limit the spread of cancers.

Lab research is an important forerunner to applied medicine

New methods of attacking cancers are dependent upon scientists understanding the genetic mechanisms involved in tumour formations and spread. Only then can the valuable laboratory-based research move forward and be applied for the greater good of patients.

I hope you found these articles interesting - please let me have your comments.

Finally, a couple of reminders :

* Don't forget the Charity Day at Battlesteads Hotel in Wark on Saturday 16 August which is being organised by Sister Karen McRae from the Stem Cell Unit at Newcastle General Hospital. Details are included in this Newsletter.

* There's not *that* many shopping days left to Christmas! Christmas cards, diaries, calendars and gifts will shortly be available from the shop in Saville Row.

Produced by North of England Cancer Research Campaign
19 Saville Row, Newcastle upon Tyne, NE1 8JE
Tel: 0191 232 5909
Charity No 1036335