



**SAMANTHA DICKSON
BRAIN TUMOUR TRUST**

Head to head with brain tumours

Research update August 2011

Systematic analysis of the role of MYCN in the formation and progression of high-grade, anaplastic medulloblastoma

Dr Louis Chesler, Institute of Cancer Research, Royal Marsden NHS Foundation Trust

Medulloblastoma is the most common malignant brain tumour in children, and is currently difficult to treat in its most aggressive (high-risk) form, in which several genes are over-activated. Understanding how these genes cause tumour growth is necessary in order to design drugs to target the genes themselves or the proteins they produce.

This study, led by Dr Louis Chesler, is examining the role and interactions of key cancer-causing genes in medulloblastoma by measuring their levels and activity at the different stages of tumour growth. MYCN is one such gene.

In collaboration with specialist laboratories in Ireland, continental Europe and the USA, the researchers are analysing which changes in gene levels and gene activity cause high-risk medulloblastoma. Interesting trends have emerged from the initial data, though further confirmatory work is needed. The team have identified the location in the brain at which tumour-initiating cells may first start to divide abnormally, enabling the researchers to analyse the genetic changes occurring at this very early stage in the disease. It is hoped that this work will ultimately help experts to determine specific targets for safe and effective new treatments.

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Research update August 2011

Systematic characterisation and functional assessment of amplified genes in paediatric glioblastoma

Dr Chris Jones, Institute of Cancer Research, Royal Marsden NHS Foundation Trust

Every year about 350 children in the UK are diagnosed with a brain tumour, and about 50 of these have high-grade gliomas (HGG) called glioblastoma multiforme (GBM). GBM is an aggressive tumour arising from the glial cells in the brain that support the nervous system, and is hard to treat effectively, due to its position in brain and resistance to cancer drugs.

In this study, Dr Jones and his team hope to make a difference to the outlook for these children by identifying the key genes underlying this disease and looking into how they work. They have begun to test a panel of 80 drugs against cells derived from the Institute's unique collection of primary brain tumours. This has enabled them to determine the best conditions in which to grow and test the cells, and has also provided clues as to which drugs may be effective against the cells. The team will now screen the cells for 'amplified' genes i.e. those genes that are present in increased numbers of copies. This will allow them to develop the current genetic 'maps' of childhood GBM. They will then explore the role of these genes by blocking their activity in GBM cells, and observing the effects.

Their findings will provide a valuable resource for the development of specifically targeted drugs for children with GBM, enabling scientists to make a real impact on improving outcomes for children with this disease.

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Research update August 2011

Molecular-Genetic and Epigenetic Analysis of Pilocytic & Pilomyxoid Astrocytomas and Ependymomas

Professor Peter Collins, University of Cambridge

Professor Peter Collins and his team are using a variety of the latest laboratory techniques to examine the genetics of three childhood brain tumour types in this project, funded by a grant generously given to SDBTT by GlaxoSmithKline.

Abnormalities that can develop in the genes within a cell can lead to the cell dividing in an uncontrolled way, resulting in a tumour. Studying these abnormalities could lead to the discovery of targets for new treatments, and identify tests to enable experts to confidently diagnose tumour type at an early stage.

The use of similar techniques led Professor Collins to discover a rearrangement of the genetic code that is present in around two-thirds of all cases of pilocytic astrocytoma, the most common primary benign brain tumour in children. He has now identified the same rearrangement in the majority of pilomyxoid astrocytomas, suggesting that these tumours are actually variants of pilocytic astrocytomas, rather than separate entities. He has developed a rapid test for the rearrangement, which allows its detection in samples removed from patients during surgery, and may aid diagnosis.

The team are screening over 28,000 genes in both pilocytic astrocytoma and ependymoma brain tumours for comparison with genes from normal (non-tumour) brains, with the aim of identifying key genetic abnormalities. These abnormalities may then be targeted by new treatments to block over-active cancer-causing genes, or re-activate other genes that, in healthy brain tissue, work to prevent cells from dividing uncontrollably. It is hoped that this project will lead to further breakthroughs in the understanding both in this tumour type, and in pilomyxoid astrocytoma and ependymoma tumours.

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Research update August 2011

Rates of psychiatric illness in long term survivors of early childhood brain tumours

Dr Howard Ring, University of Cambridge

This nationwide study, led by Dr Howard Ring, is looking at the prevalence of psychiatric illness in adult survivors of childhood brain tumours.

SDBTT is supporting Dr Ring to investigate this area, with the aim of helping both paediatric neuro-oncologists and families to be better informed about the possible long-term outcomes when making decisions about treatments for children with brain tumours. The aims of the research are to assess what psychiatric conditions are present in a group of long-term survivors of childhood brain tumours, and to see how rates of the same conditions compare in their brothers and sisters, and in the general population. This will allow the researchers to determine the extent to which brain tumours and their treatments contribute to the development of psychiatric disease later on. With the support of the National Mental Health Research Network, a project website is also being developed.

The team has so far completed assessments of 87 patients and 44 of their siblings. Preliminary results show higher rates of clinical apathy in brain tumour survivors. This is likely to be a significant problem for these patients, and could interfere with their progress in rehabilitation, education and employment. There is a range of treatments available that can be used to minimise this, however, but only if the condition is identified correctly.

The results of the study will be invaluable for giving families and health professionals an indication of the extent to which they need to consider potential psychiatric consequences when deciding on tumour treatments for a child.

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Research update August 2011

Genome-wide molecular characterisation of supratentorial primitive neuroectodermal tumour (sPNET) II

Professor Richard Grundy, University of Nottingham

In this study supported by Samantha Dickson Brain Tumour Trust, Professor Richard Grundy and his team at the University of Nottingham are investigating the genetics of a group of high-grade brain tumours known as Central Nervous System Primitive Neuroectodermal Tumours, or CNS PNETs, which include medulloblastoma. These tumours are mainly found in children, and currently have a poor prognosis, as treatment strategies are relatively ineffective and have many side effects.

In a previous SDBTT-funded study, the team examined the genetics of a large sample of CNS PNET and pineoblastoma tumours. This identified several genes that may be involved in the formation and progression of these tumours, and they are now investigating how these genes work.

In addition, working with colleagues at the Hospital for Sick Kids in Canada, the team has tested the level of molecules called miRNAs in a large collection of CNS PNET tumours; changes in the levels of miRNAs have recently been implicated in cancer.

They will now combine their findings with those from other researchers in the field, allowing them to produce a more complete 'molecular map' of CNS PNET tumours. This paves the way for the development of tests and therapies that in future could be used to better diagnose and treat children affected by CNS PNETs.

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Research update August 2011

The molecular basis of childhood medulloblastoma: from genomics to improved therapies

Professor Steven Clifford, Newcastle University

The purpose of this project, led by Professor Steve Clifford, is to investigate how changes to cells, other than those that occur in the underlying DNA sequence, affect the development of medulloblastoma, the most common malignant childhood brain tumour. The study is also looking at how these changes, called 'epigenetic events', may be used as diagnostic markers or indicators to help determine the prognosis of the disease.

Professor Clifford is particularly interested in identifying genes which show evidence of methylation-dependent control. Methylation is a chemical process involved in controlling gene activity, and Professor Clifford has been looking at the potential of methylation events to identify distinct disease subgroups of medulloblastoma.

Professor Clifford has undertaken investigations across the whole human genome, revealing a more extensive and complex medulloblastoma 'epigenome' than was previously thought to exist. His research has also provided strong evidence that the methylation status of specific genes may contribute to the biological sub-classification of medulloblastoma into different groups with different disease characteristics and prognosis, and provide potential targets around which to design better, safer treatments in future.

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Research update August 2011

A feasibility study of real-time biological characterization of medulloblastoma

Professor Steven Clifford, Newcastle University

Professor Clifford is working on a biological study to establish the feasibility of systems that will enable the rapid consent, collection, transportation and analysis of samples from patients diagnosed with medulloblastoma. Medulloblastoma is the most common malignant brain tumour of childhood, and accounts for around 10% of all childhood cancer deaths. Despite recent improvements in survival rates, the delivery of individualised therapies based on the degree of disease-risk in each case remains a major goal.

The overall aim of this study is to ensure that systems are in place ready for forthcoming pan-European clinical trials in medulloblastoma. These trials will for the first time assess the range of likely disease severity in patients, using laboratory tests on tumour samples alongside clinical measures, to select different treatment groups. This selection will underpin two concurrent trials: PNET 5, which will test whether treatment can be reduced for a sub-group of patients who have a reduced risk, and PNET 6, which will aim to improve survival rates in the standard-risk group.

Professor Clifford is working to ensure that the UK is fully represented in this study by encouraging newly diagnosed medulloblastoma patients from local Children's Cancer and Leukaemia Group Centres to register. To date, 50 patients from 12 of the 19 UK treatment centres have been registered onto the study. Laboratory analysis has been successfully completed and reported on within 30 days for 45 of the tissue samples submitted.

It is hoped that a total of 50 suitable cases will be put forward for these important trials which are due to start in 2011/12.

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Research update August 2011

Biomarker discovery for improved disease risk assessment and therapy of childhood medulloblastoma

Professor Steven Clifford, Newcastle University

This three year project led by Professor Steven Clifford started in January 2011, and is looking to further investigate the biological features of medulloblastoma and how these relate to disease progression, which could lead to better and safer treatments for individual children.

The study is using 250 medulloblastoma samples from children treated similarly on two clinical trials. Samples will be examined under the microscope and undergo comprehensive genetic analysis, the data from which will be compared with clinical information. This will enable the team to see how the biological characteristics ('biomarkers') of a tumour indicate the likely course of the disease, with the potential to help experts to select the most appropriate therapy for each child. For example, high-risk cases could be offered more intensive therapy to maximise the chances of survival, whilst reduced therapy could be given to children at lower risk in order to minimise side-effects. Furthermore, it is hoped that discovering more of the genetic changes underlying these tumours will reveal targets for new drug therapies.

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A phase II multi-centre study of the concomitant and prolonged adjuvant temozolomide with radiotherapy in diffuse pontine gliomas

Dr Simon Bailey, Royal Victoria Infirmary, Newcastle

In this Phase II study, Dr Bailey and his team are trialling a new combined chemotherapy and radiotherapy treatment schedule in children with diffusely infiltrating pontine glioma (DIPG). The study, which has completed recruitment from 14 centres around the UK, forms part of a clinical trials initiative that SDBTT is funding with Cancer Research UK. Data taken previously from the study of high-grade gliomas in adults suggests this approach may improve survival for children with DIPG.

DIPGs arise from branched cells called glia in the brain stem, the part of the brain that joins with the spinal cord. They are the most common type of brain stem glioma, which make up 10% of all childhood brain tumours.

In this study, children who have been newly diagnosed with DIPG have been given low doses of the drug temozolomide at the same time as radiotherapy, followed by further temozolomide after radiotherapy. MRI scans are being used to monitor tumour size, and children are being carefully observed for any signs of ill-health as a side-effect of the therapy, which was well tolerated by children in the preceding phase I study.

The study will provide insight into the best way forward into providing better treatment for children with DIPG. If the new treatment schedule proves safe and effective, further children may benefit from larger-scale trials in phase III.

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Research update August 2011

An Evaluation of the Tolerability and Feasibility of combining 5-Amino-Levulinic Acid (5-ALA) with Carmustine Wafers (Gliadel) in the Surgical Management of Primary Glioblastoma (GALA-5 TRIAL)

Dr Colin Watts, University of Cambridge

Glioblastoma multiforme (GBM) is the most common and most harmful primary malignant brain tumour in adults.

This study, led by Dr Colin Watts, aims to assess the safety of 5-ALA fluorescence-guided surgery in conjunction with Gliadel® for the treatment of GBM. It is co-funded with Cancer Research UK in a joint clinical trials initiative with SDBTT.

5-ALA is a drug that is converted in the body to a fluorescent chemical that accumulates in tumours. This can be seen under blue light, enabling surgeons to distinguish the borders of a tumour more precisely, allowing more accurate and complete removal of the tumour. Gliadel® wafers are biodegradable discs impregnated with the chemotherapy drug carmustine, which are implanted into the brain during surgery to release the carmustine locally where it is needed.

Gliadel® is currently used to treat GBM patients in certain circumstances, whilst 5-ALA is not yet widely available in the UK. Separately, each treatment strategy has shown survival benefits for patients with GBM. The trial has just started recruiting, and it is hoped the two therapies will prove to work together safely to improve survival rates for patients with GBM both now and in the future.

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Research update August 2011

Targeting the nuclear factor-kappaB (NF-kB) pathway to improve chemotherapy of glioblastoma multiforme

Dr Weiguang Wang, University of Wolverhampton

For patients diagnosed with a glioblastoma multiforme (GBM), the most common and most aggressive type of primary brain tumour, drug resistance can be a major obstacle to the success of their chemotherapy treatment. In this project, Dr Wang is looking at how to improve the efficacy of chemotherapy for these patients.

Many types of cancer cells are resistant to drugs because they have a high level of activity of a protein complex called nuclear factor kappa B (NF-KB), whose role is normally to help regulate the immune response to infection and disease. Some treatments therefore focus on inhibiting the activity of NF-KB; however, until now there has been little research on this approach in treating GBM. Dr Wang's research is focusing on the level of resistance of GBM cells to various drugs. His results suggest that one particular drug, disulfiram, does inhibit NF-KB activity in cells in the laboratory.

He also found that combined with disulfiram, the effects of two other drugs were also significantly improved. However, the short half-life of disulfiram in the blood stream (about four minutes) is unlikely to be long enough for it to act on cancer cells in a patient, limiting its clinical usefulness. In order to overcome this, the team has developed a new fat-enveloped formulation of the drug, which can remain stable in the blood-stream for at least 10 hours. The new formulation has demonstrated a strong anti-cancer effect on cells in the lab.

Both disulfiram and fat-enveloped drugs are already used in the clinic to treat other conditions, and so are already known to be safe for use in humans. Therefore these positive results bring the research significantly closer to clinical trials, in which disulfiram could be used to help treat patients with GBM.

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Research update August 2011

Analysis of loss of heterozygosity 1p/19q and MGMT methylation in patients with malignant gliomas

Professor Sebastian Brandner, University College London

This project, led by Professor Sebastian Brandner, involves researching three genetic tests for patients who have a malignant glioma brain tumour. The aims of the project are two-fold: to improve the accuracy of diagnosis for patients by focussing on the genetics of their tumour, and to provide doctors with important information which may indicate the likely effectiveness of chemotherapy drug treatment for individual patients. Professor Brandner has looked at the role of the MGMT gene, which is involved in cancer formation and behaviour. Differences in this gene across brain tumours affect how these tumours respond to chemotherapy; these differences can be tested for in the laboratory.

A quantitative version of this test has now been introduced, minimising the number of borderline or unclear results. A second test checks for genetic changes in oligodendroglioma tumours involving the loss of genetic material called 1p and 19q; this can help predict patient survival times. A third test for mutations in the genes *IDH1* and *IDH2* is now in place – this is used to help to differentiate between different types of glioma, to achieve more accurate diagnosis, facilitating more tailored treatment and care.

Thus far, a spectrum of molecular tests on human brain tumours has been set up and, thanks to the support of SDBTT, the National Hospital for Neurology and Neurosurgery is one of the first centres to offer these tests routinely to all eligible patients who might benefit, including referrals from other hospitals. Testing is also underway to develop and validate faster technology, which will make the results of these tests available to doctors within 72 hours.

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Research update August 2011

Establishing non-invasive biomarkers of the efficacy of novel phosphoinositide 3-kinase inhibitors in paediatric high-grade glioma by magnetic resonance spectroscopy

Dr Nada Al-Saffar, Institute of Cancer Research, Royal Marsden NHS Foundation Trust

Dr Al-Saffar has used Magnetic Resonance Spectroscopy (MRS) to look at how a new class of anti-cancer drugs for treating high-grade gliomas in children affects a specific pathway in the brain. MRS measures the levels of metabolites - the chemical 'fingerprint' that cellular processes leave behind. Dr Al-Saffar is using this technique to see how these drugs affect the levels of metabolites in a particular chemical 'pathway' in brain tissue.

Comparing treated to non-treated cells in high-grade glioma cell models, Dr Al-Saffar and her team has observed a decrease in the levels of phosphocholine (PC) and lactate; chemicals that are required for maintaining growth in cancer cells. This interesting discovery means that levels of PC and lactate could be monitored as a means of tracking the effectiveness of chemotherapy drugs, without resorting to invasive measures such as biopsies. This could have great potential for the treatment of children and adolescents with malignant gliomas, for whom invasive techniques such as biopsies can be very distressing and potentially high risk.

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Research update August 2011

Molecular genetic and epigenetic analysis of paediatric low grade gliomas

Professor Denise Sheer, Queen Mary, University of London

Professors Sheer and Ellison carried out an important study looking for genetic changes in grade I and II astrocytoma brain tumours, including pilocytic astrocytoma, the most common form of brain tumour in children.

They have found that most pilocytic astrocytomas (which are grade I) have a particular rearrangement of DNA involving a gene called BRAF; this change affects a 'pathway' involved in the uncontrolled cell replication that can lead to the growth of a tumour. A comparison of over 70 children's brain tumours of multiple types has revealed that this DNA rearrangement is unique to low-grade astrocytomas.

The researchers showed that the DNA sequences around the breakpoints in the genes have a particular pattern called 'microhomology'. This gives us information on how these important rearrangements in DNA arise.

Two other genetic mutations were also discovered in the tumour samples. The mutations affect genes that are involved in regulating the activity of other genes, and are likely to be important in tumour formation.

Each of the pilocytic astrocytoma samples tested contained one of these three genetic changes. The team also found that over one in four of the grade II tumours had genetic changes that activated the same pathway.

The research suggests that the pathway alteration is a trigger in the generation of low-grade astrocytomas. Drugs that specifically target this pathway are already being tested for use in other cancers such as melanoma, and although further research is needed, they may also be of use in treating low-grade astrocytomas in the future – particularly those that are not cured by current treatments.

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**SAMANTHA DICKSON
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Head to head with brain tumours

Research update August 2011

Advanced magnetic resonance imaging and metabolic studies of low grade gliomas of childhood

Professor Richard Grundy, University of Nottingham

Low-grade tumours constitute 40-50% of all brain tumours in children. They are a diverse group consisting mainly of gliomas, which despite their similarities in origin, can behave very differently. Treatment of gliomas is varied, and includes surgery, chemotherapy and radiotherapy; all of which present significant risks and side effects.

The development of new non-invasive tools to aid with diagnosis, prognosis and treatment monitoring is an important research goal and SDBTT is supporting Professor Grundy and his team in this project which is looking at the role of Magnetic Resonance Spectroscopy (MRS) as a non-invasive alternative to biopsy. This is especially relevant for tumour types where it is not possible to biopsy due to their location in the brain, for example tectal plate gliomas. In general, biopsy has associated risks and trauma, so non-invasive alternatives are preferable. MRS is an imaging method for obtaining biochemical profiles of tissue which has shown promise in detecting differences in paediatric brain tumours and predicting prognosis.

Advanced imaging gives important new insights into patients' tumour biology, and a further important aspect of this study is relating the results of sample analysis and microscopy in the laboratory to the imaging features produced by MRS. This three year project has been successful in attaining its goals of developing advanced magnetic resonance imaging across two major children's brain tumour centres in the UK: Birmingham Children's Hospital and Nottingham University Hospital. The results from this research will help to understand how MRS results relate to conventional biopsy-based diagnostic techniques, and how this can be exploited to further develop its use for patients in the clinic in future.

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Research update August 2011

Reassessing the origins of cranial germ cell tumours

Dr Paul Scotting, University of Nottingham

Dr Scotting's research is focussing on which neural stem cells in the brain are more likely to grow to become Germ Cell Tumours, (GCTs). Neural stem cells are generalised cells in the brain that can divide to replace themselves, or to give rise to cells that mature into more specialised cell types, and normally have a role in brain growth and repair. GCT is a type of children's brain tumour that is often overlooked by researchers, yet in some countries can account for up to 15% of all brain tumours.

Dr Scotting's research so far suggests that contrary to popular belief, these stem cells might be activated by non-genetic factors; this means that the damage done to the cells may be more readily reversible than the damage seen in most cancers. Dr Scotting and his team are carrying out experiments to determine if neural stem cells of the brain are able to give rise to GCTs, and to investigate the role of different chemical processes, such as methylation and acetylation, in this process. In particular they are looking at the effects of activating two particular genes, called Oct4 and kit, in stem cells of the normal brain, as both are implicated in the development of GCTs.

An improved understanding of which cells these tumours originate from and how this occurs could help diagnose these tumours more accurately, and provide insight into the best strategy for developing new therapies to treat them in the future.

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Research update August 2011

Clinical Trials Project Officer

Dr Susan Short, University College London

This post supports the National Cancer Research Institute Brain Tumour Clinical Studies Group (NCRI BT CSG), and is jointly funded by Cancer Research UK and Samantha Dickson Brain Tumour Trust. NCRI is a partnership between the government, charity and industry established in 2001 to develop common plans for cancer research and to avoid unnecessary duplication of effort.

The Brain Tumour CSG is chaired by Dr Susan Short, and seeks to increase access of UK brain tumour patients to quality clinical trials. Among other responsibilities, the Project Officer will work with CSG members and the UCL Cancer Trials Centre to develop trial designs, offer advice and support to potential brain tumour trial leaders, and promote clinical trials among clinicians.

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Research update August 2011

Development and evaluation of a neuropsychological follow-up service for survivors of childhood brain tumour

Dr Ingram Wright, North Bristol NHS Trust

Approximately two thirds of survivors of childhood brain tumours experience difficulties afterwards as a result of the initial tumour or treatment. Difficulties can be physical, learning, behavioural or social, and many families would benefit from specialist support to assist with these issues.

Dr Wright and his team are running an extensive three-phase project which aims to identify how to support these children in overcoming problems with memory and organisation, thereby helping them to achieve a better quality of life.

Phases one and two involve assessing difficulties experienced by these children through parent questionnaires and direct clinical assessment. Questionnaires have been sent out to 36 families, and are also being distributed to a further 120 families from the South-West region. Ten children have now undergone clinical assessments.

Phase three involves an innovative memory rehabilitation programme, and Dr Wright has identified specific children from phase two who meet the criteria for the programme. The team has successfully carried out the rehabilitation programme with two of these children, and aims to do so for ten more.

A key output for the project is an anticipated business model for the development of a regional neuropsychology service to support survivors of childhood brain tumours; the team also aims to develop a transferable resource kit for NHS Trusts interested in developing such a service in other regions.

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Research update August 2011

Central support for CCLG CNS Tumour clinical trials pathology review and biological studies: Funding of a Biomedical Scientist

Professor Steven Clifford, Newcastle University

Jointly funded with Cancer Research UK

The Children's Cancer and Leukaemia Group (CCLG) Central Nervous System (CNS) tumours division are conducting UK-based clinical trials for children with brain tumours as part of a pan-European study. Trials involve 'biological studies' and 'central pathology review' (CPR) which entail performing molecular and microscopic studies on tumour samples from trial patients. This presents unique challenges, as tissue samples must be collected, stored, processed and analysed, requiring the coordination and input of a skilled biomedical scientist. SDBTT is jointly funding this crucial support role with Cancer Research UK, to help ensure patients and scientists gain maximum benefit from these clinical trials.

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Research update August 2011

Clinical fellowship in neurological neuro-oncology

Dr Robin Grant, University of Edinburgh

Dr Robin Grant supervised Dr Kerrigan during his SDBTT-funded Clinical Fellowship Year at the Edinburgh Centre for Neuro-oncology, Western General Hospital. This clinical training year is vital for identifying, encouraging and training neuro-oncologists of the future. The Fellowship provides a broad structured advanced neuro-oncology curriculum, in a multidisciplinary neuro-oncology unit, and through a short training attachment in one of the best neuro-oncology units in the world, ensuring that excellence in neuro-oncology in this country is safeguarded and encouraged for the future.

Incorporated in Dr Kerrigan's training was broad and in-depth exposure to outpatient clinics, seeing patients on the wards as well as patients who are attending hospital for treatment. The Clinical Fellow is an active part of the neuro-oncology team and Dr Kerrigan played an active role in developing a number of research ideas in the field of neuro-oncology, with a particular emphasis on the management of seizures in people with brain tumours.

Dr Kerrigan recently underwent his six weeks training attachment in the department of neuro-oncology at UCSF in San Francisco, one of the world's leading neuro-oncology centres. This provided an invaluable opportunity to gain experience in the use of a range of different cutting-edge brain tumour treatments and imaging techniques.

He will now spend a two year period of brain tumour research before completing general neurology training; as a direct result of this opportunity, Dr Kerrigan is now committed to pursuing a career in neuro-oncology, helping more brain tumour patients in the future.

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**SAMANTHA DICKSON
BRAIN TUMOUR TRUST**

Head to head with brain tumours

Research update August 2011

Genome-wide analysis of ependymomas and pilocytic astrocytomas

Professor Peter Collins, University of Cambridge

Around 145 children are affected by pilocytic astrocytoma tumours each year in the UK, a quarter of which cannot be successfully treated. Professor Peter Collins recently led on a major research project that pinpointed a rearrangement of DNA that causes around two-thirds of all cases of pilocytic astrocytomas – the most common brain tumour in five to 19 year-olds.

This research identified additional copies of whole chromosomes in a number of cases, including a chromosome that is commonly altered in other types of astrocytoma. In addition, Professor Collins found a small region of one chromosome that is rearranged, leading to the production of an oncogene – a gene that codes for a cellular component and is permanently switched on – which causes cells to grow and multiply.

This discovery is specific to pilocytic astrocytoma, and is the first time this type of cell activity has been associated with a brain tumour. It is hoped that these findings will make it possible to design therapies in the future that block the activity of the malfunctioning gene and halt the growth of tumour cells.

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**SAMANTHA DICKSON
BRAIN TUMOUR TRUST**

Head to head with brain tumours

Research update August 2011

Imaging of molecular dynamics and cell fate to identify new targets for medulloblastoma therapy

Dr Violaine Sée, University of Liverpool

An important part of treating brain tumours and an area of particular focus for SDBTT is not only to increase survival rates, but also to improve the quality of life of survivors. Dr See's research has focussed on treating children with brain tumours while trying to reduce the toxic side effects of drugs such as chemotherapy. Her team has looked at the molecular mechanisms regulated by the drug etoposide, to monitor cell sensitivity in several medulloblastoma and glioblastoma cell lines, the two main types of brain tumours.

In some medulloblastoma cells, Dr See and her team found mutations in two molecules called p53 and nuclear factor kappa b (NF- κ B). These molecules play an important role in the cell death/survival balance of the cells, and their mutation can make cells resistant to a chemotherapy drug called etoposide. Their results strongly support the relationship between chemotherapeutic drug sensitivity and the genetic make-up of the tumour. This interesting discovery may help lead to individually tailored treatments plans, in which each patient's molecular 'fingerprint' is taken into account, thereby helping doctors to choose the treatments for each patient that will be most effective for them, whilst minimising harmful side effects.

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**SAMANTHA DICKSON
BRAIN TUMOUR TRUST**

Head to head with brain tumours

Research update August 2011

Detailed analysis of two genetically altered regions of the genome in astrocytic gliomas by means of chromosomal tile path array - comparative genome hybridisation

Professor Peter Collins, University of Cambridge

The aim of this project, led by Professor Collins, was to record the losses and gains of genetic information on two chromosomes (#7 and #10) in all malignancy grades of adult astrocytic tumours (chromosomes are structures found in cells that contain our genes). Astrocytic tumours are the most common type of glioma and develop from star-shaped cells called astrocytes. They can affect both adults and children, and usually develop in the main part of the brain, known as the cerebrum.

Through his research, Professor Collins identified an extra copy of part of one chromosome (10p), which was found almost exclusively in the less malignant forms of these tumours; he also discovered differences in survival rates of patients with this extra copy of 10p.

These findings will ultimately help us understand the mechanisms by which these tumours arise, and it is hoped they will lead to improvements in diagnosis and prognostication. They could also provide targets for new specific targeted molecular-therapies in the future, and provide a good foundation for further genetic studies.

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**SAMANTHA DICKSON
BRAIN TUMOUR TRUST**

Head to head with brain tumours

Research update August 2011

A genome-wide methylation analysis of oligodendroglial tumours

Dr Koichi Ichimura, University of Cambridge

In this study, Dr Ichimura and his team have investigated the role of a particular gene, IDH1, in the early development of 600 brain tumours of different types. They found that mutations of the IDH1 gene occur in the majority of astrocytomas, oligodendrogliomas, mixed gliomas and secondary glioblastomas, but rarely in primary (non progressive) glioblastomas, and never in any other types of brain tumours. Their findings suggest that the IDH1 gene may play an important role in the early formation of astrocytomas, oligodendrogliomas and mixed gliomas. It is hoped that this research into the IDH1 gene will have significant implications for both the understanding and precise diagnosis of brain tumour types.

The team also used a technique called 'pyrosequencing' to examine the structure and workings of a gene called 'MGMT'. Methylation of MGMT in high-grade gliomas is known to affect their sensitivity to temozolomide drug treatment, and is sometimes tested for in these patients. Methylation is a chemical process involved in gene control. Dr Ichimura has found that in fact only a specific portion of the MGMT gene needs to be methylated in order to confer this sensitivity.

In addition, the team looked at the role of DNA methylation more broadly - and whether it may de-regulate certain genes, leading to the formation of a tumour. They successfully identified a number of other new genes potentially involved in tumour development, and these could be used as new diagnostic markers for exact tumour type, or as targets for new therapies.

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**SAMANTHA DICKSON
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Head to head with brain tumours

Research update August 2011

Epigenetic silencing of gene expression in paediatric intracranial ependymoma

Dr Tracy Warr, University College London

Ependymomas are a rare type of glioma, which develop from the ependymal cells which line the ventricles (fluid-filled spaces in the brain), and from the central canal of the spinal cord. The prognosis for paediatric patients with ependymoma remains poor. These tumours often recur following treatment, and five-year survival rates are only 50%. Little is understood about the genetic processes and abnormal changes within cells which control the behaviour of these tumours in patients.

In this project, Dr Warr and her team built on their previous work that looked at the effect of gene silencing – the ‘switching off’ of a gene by cellular mechanisms. They identified a tumour suppressor gene on chromosome 22 which is turned off in 60% of ependymomas. Furthermore, they demonstrated that an important mechanism for silencing the expression of multiple genes in ependymoma is through DNA methylation, which is a process involved in gene regulation.

Dr Warr is hopeful that by gaining a better understanding of the genetic factors which contribute to ependymoma, more effective, targeted treatments for patients diagnosed with this rare tumour type can be developed.

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**SAMANTHA DICKSON
BRAIN TUMOUR TRUST**

Head to head with brain tumours

Research update August 2011

The contribution of drug resistant cancer stem cells to paediatric brain tumours

Dr Elizabeth Coyle, University of Nottingham

Children's brain tumours often show a poor long-term response to chemotherapy, and in this SDBTT-funded project, Dr Coyle has looked at whether a specific part of the tumour containing 'cancer stem cells' is causing this poor response, and how it may do this.

Looking at cell lines (lab-cultivated cells) from several types of brain tumour, including ependymoma, medulloblastoma, oligodendroglioma and high-grade glioma, Dr Coyle's team set out to identify and characterise cancer stem cells from within these lines and determine their level of drug resistance. Results showed that cells contained a sub-population of cancer stem cells which were able to rapidly form tumours. Furthermore, this sub-population was more resistant to the cancer drug etoposide than the rest of the tumour.

Further investigation found that these cells had surface 'pumps' – known as ABC transporters – which removed the drug from the cell, explaining the cells' resistance to drug therapy. Importantly, the team was also able to demonstrate in the laboratory that this drug-resistant trait could be overcome if a specific ABC transporter, ABCB1, was blocked. Moreover, they found that the survival time for chemotherapy-only patients whose tumours contained cancer stem cells with ABC1 was half that for patients with no ABC1.

This research has led to a greater understanding of both the basic biology of paediatric brain tumours, and of the way in which chemotherapy affects them. In future, ABC-inhibitors may be used to treat childhood brain tumours to restore the effectiveness of conventional drug therapy, thereby improving outcomes.

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**SAMANTHA DICKSON
BRAIN TUMOUR TRUST**

Head to head with brain tumours

Research update August 2011

Comprehensive mapping of gene expression and genomic gains and losses in paediatric high grade gliomas

Professor Richard Grundy, University of Nottingham

Treating paediatric high-grade gliomas (HGGs) represents a formidable challenge as conventional therapy combinations cure fewer than 20% of children with this disease. Professor Grundy's research in this area has made important in-roads into achieving a greater understanding of the underlying biology of paediatric HGGs, on which new therapies can be based.

In this SDBTT-funded project, Professor Grundy and his team defined the most common and significant genetic abnormalities in paediatric HGGs, having performed genetic profiling on nearly 40 HGG tumours, including 13 brain stem gliomas. They confirmed that the genetic alterations found in adult HGG are rarely seen in the childhood form of the disease, indicating that it requires a different approach is required.

The data generated from this project will be combined with that from researchers in France, providing a vital resource to help investigate HGG tumour sub-classifications. This will enable the identification of key genes and pathways present in paediatric HGGs, aiding the future development of new treatments for this condition.

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**SAMANTHA DICKSON
BRAIN TUMOUR TRUST**

Head to head with brain tumours

Research update August 2011

Wnt signalling in neural stem cell differentiation and tumourigenesis of the central nervous system

Professor Sebastian Brandner, University College London

Medulloblastoma is a highly malignant brain tumour in children and this research project, led by Professor Brandner, looked at how these tumours arise from the stem cells in the brain, and how different mutations of these cells cause different types of brain tumours.

Professor Brandner and his team focused on a particular network of proteins known as the Wnt Signaling Pathway, already well known for its role in cancer, and looked at what happens when the signaling deviates from its usual pattern.

They successfully developed and characterised a laboratory cancer model for brain tumours, and have developed the basis of a model with which the effects of alterations in this pathway may be studied.

Their results suggested that medulloblastoma tumours do originate from brain stem cells, and that certain combinations of mutations in these cells cause other different types of brain tumours, including glioma. In contrast, they found that tumours do not appear to originate from a type of cells called astrocytes.

The cancer models that have been developed in this project will provide a new tool in the armory of scientists with which to further study the origins and development of different brain tumour types, which is key to understanding how best to distinguish and treat them in future.

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**SAMANTHA DICKSON
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Research update August 2011

Two trial coordinators and a statistician for Children's Cancer and Leukaemia Group Clinical Trials Unit

Professor Sue Ablett, University of Leicester

Professor Ablett and her team, with a grant from SDBTT, provided invaluable statistical support to the Central Nervous System division of the Children's Cancer and Leukaemia Group (CNS CCLG) Clinical Trials Unit. CNS CCLG is an association of healthcare professionals that is committed to improving treatment for children with brain tumours.

A dedicated statistician, Dr Bujkiewicz, was employed for this project, and analysed information collected from previous and ongoing clinical trials in the field of childhood brain tumours, covering most of the main childhood brain tumour types.

Dr Bujkiewicz analysed and fed back live data to the Chief Investigators in each trial, ensuring the trials' safe and effective continuation, and contributed significantly to the design of subsequent trials. Based on this research, the team has published two scientific papers and presented their findings to national and international audiences, including scientists in the USA, France and Spain. Details of some of the studies which Dr Bujkiewicz worked on, made possible by funding from SDBTT, are provided below:

1. Statistical analysis and interpretation of data from clinical trials and audits:

1. High dose Tamoxifen in children with diffusive pontine gliomas (CNS 1999 06)
2. Brain Stem Glioma (CNS 1990 06)
3. HART for Metastatic Medulloblastoma (CNS 2001 06)
4. Low Grade Glioma (CNS 1997 02)
5. Relapsed Ependymoma (CNS 2001 04)
6. SIOP Ependymoma (CNS 1999 04)
7. High Grade Astrocytoma (CNS 1995 01)
8. Nutrition audit – children with Medulloblastoma from 3 CCLG centres

2. Contribution to study design:

1. Infant Ependymoma II (CNS 2007 09)
2. Phase II Methotrexate in children with Ependymoma (CNS 2005 03)
3. Brain Stem Glioma Temozolomide (CNS 2007 04).

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**SAMANTHA DICKSON
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Research update August 2011

UK case control study of possible causes of brain tumours in children, teenagers and young adults: a pilot study

Professor Patricia McKinney and Professor Jillian Birch, Universities of Leeds and Manchester

While there are clear environmental risk factors for cancer of the lung and colon, further research is desperately needed into what causes brain cancer. Evidence is growing for the role of environmental and genetic factors in triggering brain tumours in young people. This study, supported by SDBTT, was established as the pilot for a large-scale study of brain tumours in children, teenagers and young adults, with the aim of helping to identify the causes of these tumours.

Professors McKinney and Birch designed and conducted interviews with 50 case families in which a child had been diagnosed with a brain tumour and 78 control families with a healthy child. Whilst sourcing willing families within the NHS structures was a challenge, techniques were developed and documented to successfully overcome this. The study included questions on maternal experiences during pregnancy, birth details, childhood illness, mobile phone use and family history of disease and cancer, as well as day care attendance and social contacts. Any trends that emerge following the final analysis may provide clues as to the possible causes of brain tumours. Most case families were pleased that studies investigating this were being done, and welcomed the opportunity to be involved. There was also a clear consensus among participants in favour of taking blood or saliva samples to aid future molecular epidemiological research in to the causes of brain tumours.

This project has also acted as a pilot for the CEFALO study, an international case-control study of the relationship, if any, between mobile phone use and the risk of brain tumours in children and young adults, the results of which should be published later this year. The project has also provided a solid basis in terms of methodology and preliminary trends for a larger international study (currently being set up) into the causes of brain tumours in children and young people.

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**SAMANTHA DICKSON
BRAIN TUMOUR TRUST**

Head to head with brain tumours

Research update August 2011

In depth study over time on effect of child and parent factors on perceived quality of life of children treated for a brain tumour (initial and follow-on study)

Professor Colin Kennedy, University of Southampton

Children treated for a brain tumour can suffer a significantly reduced quality of life, and improving outcomes for these children is an important goal for SDBTT. In this study, Professor Kennedy is examining the effect of child and parent factors over time on the perceived quality of life of children treated for a brain tumour. The study has involved a sample of 110 children aged 8-14 years, all diagnosed within a three-year time period, with either a medulloblastoma or a low-grade cerebellar astrocytoma tumour. These children were compared against a control group of children with no history of a tumour, all from the same schools. All the children were assessed on three occasions over a two-year period. Professor Kennedy and his team have also included observations from parents and teachers in order to get a greater understanding of the ongoing difficulties facing children at home and at school.

Preliminary results suggest that there are some important differences between the three groups in terms of quality of life, health and IQ, and that the factors affecting these differences change as time goes on. The study also shows that the children diagnosed with brain tumours had more difficulties at school, both in terms of school work and their behaviour. Further analysis of the data at all three time points during the study will enable Professor Kennedy to make specific recommendations on how to avoid or reduce the difficulties that these children experience both at home and at school, and to improve their overall quality of life.

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