Report of the Task and Finish Working Group on Brain Tumour Research

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Prepared by the Task and Finish Working Group on Brain Tumour Research

Convened by the Department of Health and Social Care

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Preface

Peter Realf was a patient representative on the Working Group. Peter is father to Maria Lester whose 2015-2016 e-petition led to 120,129 signatures, a Petitions Committee Inquiry, Report, and Westminster Hall Debate with over 70 MPs in attendance. George Freeman MP, then Minister for Life Sciences, committed to the establishment of the Working Group. Peter said:

“A brain tumour diagnosis is devastating for both the patient and their family. As well as the inevitable fears about survival, in many cases life suddenly becomes a round of tests and appointments, often followed by invasive surgery that may leave patients with severe problems such as seizures.

Losing a loved one to this particularly cruel cancer is heart-breaking – whether it is a small child you will never see grow, or an adult parent or partner you have shared your life with. In my case I lost my only son Stephen, the youngest of three children, who was diagnosed with an astrocytoma aged just 19.

Overnight he lost his promising career as an RAF pilot, his driving licence and his independence, but what hit us most was his loss of *hope*. We were told by his neuro-surgeon: “This will never have a happy ending.” Stephen survived for another six years, making him one of the “luckier” brain tumour patients, since more than 80% will die within five.

As his condition deteriorated, our previously super-fit young man was unable to walk 10 feet from his bedroom to the bathroom. Later, he lost the ability to speak, to eat, and then even to swallow. Others lose their sight, balance, hearing or memory. Stephen passed away at home in 2014 and our lives will never be the same again.

After his death, our family set out to learn more about brain tumours and were deeply shocked to discover that it is the biggest cancer killer of children and those under 40, yet it received only 1.37% of the funding for research into cancer. How can this be?

I would earnestly ask the Minister to champion the urgent need for increased funding with the Government, so that ultimately a cure may be found, but equally importantly, those living with a brain tumour now, can be given much-needed hope.

While I also endorse the need to improve earlier diagnosis, this alone without a cure will simply mean that patients face a longer walk to the grave.

As the Petitions Committee Report summarised; “Successive governments have failed brain tumour patients and their families for decades. The Government must now put this right.”

It has been a privilege to represent the brain tumour community, alongside Sue Farrington-Smith, Chief Executive of Brain Tumour Research - the leading supporters of my daughter's petition. It has been encouraging to witness the Working Group discuss the opportunities for research into brain tumours, the barriers which currently exist, and the areas that deserve focus. Momentum really does appear to be gathering, with new initiatives to improve outcomes for brain tumour patients and their families being announced. The proof of the effectiveness of the Working Group is yet to come when we see the Government with larger cancer charities raising investment to in line with our

2015-2016 petition to give spending on research into brain tumours parity of funding with other cancers."

Summary and actions

A brain tumour diagnosis is devastating for a person, and their family and friends. Brain tumours are difficult to treat, not only because of their physical location where it is crucial but difficult to minimise damage to normal tissue, but also because the body's natural protective brain filter, the blood-brain barrier, shields tumours from drugs. These are also some of the main reasons why brain tumour research is so difficult. This is reflected in the relatively low numbers of research applications received by funders.

In 2015-2016 an e-petition to increase funding into research on brain tumours led to 120,129 signatures, a Petitions Committee Inquiry, a report, and a Westminster Hall Debate with over 70 MPs in attendance. George Freeman MP, then Minister for Life Sciences, agreed that more needed to be done, and announced the formation of a Department of Health Task and Finish Working Group.

The Working Group was chaired by Professor Chris Whitty, the Department of Health Chief Scientific Adviser, and brought together clinicians, charities, a patient carer, and officials to discuss how, working together with research funding partners, the need to increase the level and impact of research into brain tumours could be addressed. This is the first time that research funders have come together to discuss how this difficult area might be moved forward.

The Working Group agreed that, although the availability of funding for brain tumour research may not be the principal problem today, in the past it has been a major barrier. All are now agreed that additional research is needed and funders stand ready to invest more in brain tumour research.

Following such a prolonged period of under-funding, the principal issue is the relative lack of fundable research applications currently being received, compared to the clear need, which occurs for many reasons and needs to be tackled systematically. Therefore, the Working Group focused on identifying opportunities for removing barriers and generating additional high quality research applications.

The Working Group met four times face-to-face, and also electronically, and obtained input from external experts. The Working Group came to the main conclusions set out immediately below. Following the Working Group's report, funders will convene to discuss how to respond.

a) An effective way of growing research capacity and capability at all career stages, including senior research leadership, is to establish dedicated brain tumour research centres. Brain Tumour Research and The Brain Tumour Charity are already funding such centres. Cancer Research UK (CRUK) has released a call for applications for up two large centres.

b) Another way to encourage brain tumour research is for funders to state explicitly to the research community that research applications in this area are particularly welcome. Specific research areas that could be highlighted are included throughout this report, including detection, pre-clinical models, radiotherapy, surgery, drug development, and clinical trials. To support the aims of this report the Department of Health's National Institute for Health Research (NIHR) will announce a highlight notice to encourage research into brain tumours across its programmes in summer 2018.

c) Researchers need access to appropriate brain tumour tissue and blood samples with accompanying clinical data. Current sample collections are not optimal, in terms of their size and nature, for the latest research needs. Brain Tumour Research, The Brain Tumour Charity, and the Medical Research Council will work with relevant stakeholders to help ensure maximum use of existing brain tumour tissue collections and build further capacity. Community leadership and co-ordination will be important.

d) The UK has great strengths in neuroscience research, but the current link-up to the brain tumour agenda is limited. There are significant opportunities for the brain tumour research community to link up with this excellent research to help tackle some of the key research questions. The MRC and Brain Tumour Research will jointly develop a Workshop to bring the UK brain tumour and neurosciences research communities together to explore areas of common interest and opportunities for new research activities.

e) Certain drugs that have been developed for indications other than brain tumours may have some effectiveness against brain tumours. There are a range of issues in developing such 'repurposing' of drugs. The Association of Medical Research Charities, alongside the Department of Health, has brokered a number of meetings with a wide range of stakeholders to address drug repurposing when sufficient evidence is available to support its use in a new indication. It will be important for these recommendations to be embraced.

f) James Lind Alliance (JLA) Priority Setting Partnerships (PSP) agree research priorities that are important to patients and clinicians. The JLA in Neuro-oncology PSP has developed the top 10 important research questions in brain tumours. CRUK has developed a top 10 of research priorities through extensive consultation with the research community. All of these should be embraced by researchers and research funders.

g) For research opportunities to flourish, it is imperative that dedicated training for doctors involved in the diagnosis and treatment of brain tumours exists and that time is provided in consultant posts to allow research to be undertaken. This is particularly true of medical oncology – there is currently only one medical oncologist specialising in this field in the UK. Royal Colleges currently not providing dedicated sub-specialism for neuro-oncology should consider sub-specialty training within their curricula. NHS Trusts should consider dedicated neuro-oncology consultant posts within the fields of neurosurgery, neurology, neuropathology, paediatrics, and medical and clinical oncology.

h) Brain tumours are relatively rare and the brain tumour research community is small, being spread across multiple different health professions and scientific disciplines in both academia and industry. Therefore, more co-ordination and co-operation within the

research community is essential to accelerate progress in brain tumour research. The brain tumour research community should come together to identify clear mechanisms to improve co-ordination and collaboration in the field. Where additional funding would be required to support this, the development of unified, bold, clear and costed proposals will enable funders to consider these and respond accordingly.

i) People with brain tumours have made it clear that they want their health data to be used for research to accelerate the development of new treatments. Following the response to initiatives such as care.data, many researchers and analysts report having found it more difficult to access data in a timely manner. Regulators should respect the wishes of patients for their data to be used in research. NHS Trusts and arms-length bodies should collaborate with medical research charities to enable them to meet the wishes of patient groups whom they represent in issues related to wider access to data.

1. Background and introduction

The diagnosis of a brain tumour will have implications on long term quality of life for many of those affected. For thousands of people a brain tumour is a part of living, an aspect of their present and future. Unlike tumours in other areas of the body, brain tumours affect the characteristics and facilities that make people individuals. It affects the part of you that makes you 'who you are', and change may be radical and permanent. Many people affected speak of a sense of losing an aspect of oneself. Around a third of people affected will experience personality changes and one in two will experience memory loss. Many feel like their body is betraying them. Around a third of people with a brain tumour are likely to experience mobility problems and three in five will experience fatigue. Mental and physical decline can limit independence and career and educational opportunities. Three in four will lose their driving licence at some point, one in two people affected face financial difficulty and around 30% of those affected give up work entirely. There is also a toll on emotional health, interpersonal relationships and intimacy which accompanies such profound changes.

Brain tumours are also the biggest cancer killer of children. But thousands of children and young people face a difficult present and an uncertain future. Many will live through childhood and into adulthood with the burden of the symptoms of their tumour and/or treatment. Symptoms can disrupt mental and physical abilities in the short and long term. Over a third of children and young people affected will experience difficulties with thinking, concentrating and processing information. Many will struggle to varying degrees with balance, co-ordination, movement and walking. Their peers may not fully understand what it is like and many young people will have difficulty finding their place. A brain tumour will have a negative impact on relationships with friends for around three in five children and young people affected. Play and social interaction is integral to a child's development, yet around two thirds of children will miss out on playing with other children. At a young age, independence, social interaction, and carer and educational opportunities help shape life to come. These opportunities may be limited by the diagnosis of a brain tumour. The impact on quality of life of the parents and carers must also not be forgotten. For around three quarters of parents their child's brain tumour will have a moderate or severe impact on their own mental health.

The Minister for Life Sciences announced the formation of a Task and Finish Working Group at a House of Commons Debate on brain tumours on 18 April 2016. The Debate followed the report of the House of Commons Petitions Committee Inquiry into 'Funding into research for brain tumours'[(1)], which was published on 14 March 2016. The Petitions Committee Inquiry followed an e-petition that resulted in 120,129 signatures. The Government's response to the Petitions Committee report was published on 16 June 2016.

The Working Group was tasked to bring together clinicians, charities, patients, and officials to discuss how, working together with research funding partners, the need to increase the level and impact of research into brain tumours could be addressed. The Terms of

Reference are at Appendix 1. Professor Chris Whitty, Department of Health Chief Scientific Adviser, chaired the Working Group. The membership is at Appendix 2. The Working Group met face-to-face on four occasions between October 2016 and July 2017 with additional electronic discussions.

The Working Group agreed to exclude secondary metastases from its scope.

There are over 100 different types of brain tumour.

- Around three in 20 (14%) people diagnosed with a brain tumour survive their disease for ten years or more.
- 80.1% of people diagnosed with a brain tumour die within five years.
- More than two-thirds (68%) of children diagnosed with a brain tumour survive for at least 10 years.[2]

Brain tumours kill more children and adults under the age of 40 than any other cancer.

- They kill more children than leukaemia
- They kill more men under 45 than prostate cancer
- They kill more women under 35 than breast cancer

71% of those who die of a brain tumour, die under the age of 75 compared to 46% for all cancers.[3]

Members of the Working Group compiled a 'map' of current UK brain tumour research activity as set out in Appendix 3.

The Working Group also highlighted the major infrastructure investments in cancer research and beyond (eg imaging and biobanking) that provides crucial underpinning support for tackling the needs and opportunities in brain tumour research. Summaries of key investments from the major national funders are presented in Appendix 4.

The Working Group agreed that, although the availability of funding for brain tumour research may not be the principal problem today, in the past it has been a major barrier. All are now agreed that additional research is needed and funders stand ready to invest more in brain tumour research.

Following such a prolonged period of under-funding, the principal issue is the relative lack of fundable research applications currently being received, compared to the clear need, which occurs for many reasons and needs to be tackled systematically. Therefore, the Working Group focused on identifying opportunities for removing barriers and generating additional high quality research applications.

2. Opportunities

2.1. Biobanking

As routine practice, a biological sample of a tumour is taken during surgery to accurately determine the tumour type and potential prognosis. In a research setting, the analysis of biological samples, linked to clinical data, is critical in accelerating the understanding of tumour biology and helps in the identification of new targets for treatment. The majority of patients have indicated they would be willing for samples from their tumour to be used for research following surgery. Surgery, and the subsequent opportunity to sample tumour material, is not always an option for patients due to the high risks involved. Moreover, each sub-type of the disease is relatively rare further limiting opportunities to collect the number of samples required to form meaningful, adequately-powered studies.

Whilst formalin-fixed and paraffin-embedded ('FFPE') pathology samples from the archives of 26 NHS Neuropathology Centres are available quite comprehensively through the BRAIN UK network,[(4)] these types of samples allow for only limited analysis. Snap frozen tissue samples need to be collected and made available to researchers in order for them to carry out the in-depth molecular analysis required to accelerate understanding of tumour biology. This distributed bank, whilst being restricted to FFPE samples which may not be appropriate to answer all of the research questions posed, does give effective coverage to 90% of the existing brain tumour pathology samples available within the UK. Furthermore, for paediatric brain tumour samples, collection is embedded in clinical practice across UK centres. The Children's Cancer and Leukaemia Group (CCLG) Tissue Bank co-ordinates centrally and offers a single point of access for researchers. The relatively small number of cases of childhood cancers has made this process easier.

The active collection of adult brain tumour samples in a prospective format for research is not routine across all UK centres or co-ordinated nationally and there is no centralised access for researchers. In a recent survey of neurosurgical units by the Society of British Neurological Surgeons, 60% of the 29 respondents confirmed that snap frozen tissue samples were banked whilst only 40% also collected blood samples. This results in the level and impact of research that can be conducted being limited.

There is an opportunity, complementary to existing approaches, to develop a longitudinal adult brain tumour bank with centralised access for researchers. This could be part of a prospective cohort study which will additionally build infrastructure in clinical trials and should include a complete sample set of all relevant formats (fresh and frozen tissue, blood, and plasma), supporting clinical annotation and featuring uniform collection protocols.

Collection of such a bank should be linked to the work of Genomics England to ensure genotyping data is available for the majority of samples submitted. There is already rich learning from the 100,000 Genomes Project, for example that fresh-frozen samples are needed for whole genome sequencing. NHS England has been developing the

commissioning of genomic services, including optimising the diagnostic pathway by incorporating the taking and processing of adequate biopsy samples.

Brain Tumour Research, The Brain Tumour Charity, Cancer Research UK, and the Medical Research Council will convene a stakeholder meeting to discuss use of existing brain tumour tissue collections and build further capacity, with a strong action plan and recommendations.

2.2. Neurosciences and brain development

The UK has great strengths in neuroscience research. There are significant opportunities for the brain tumour research community to link up with this excellent research to help tackle some of the key research questions.

Developmental neurobiology is a long-standing research strength of the UK. Deciphering how the brain develops is vital to understanding brain tumours, as the tumours – particularly those in children and young adults – may arise from corrupted neural stem cells and progenitors. Stem cell biology is also strong in the UK, with infrastructure and investment to exploit many state-of-the-art technologies including: single cell analysis, '-omic' approaches, genome editing and organoid culture systems. These provide an opportunity for new disease-relevant human experimental model systems and there is a clear opportunity for brain tumour researchers to link up with developmental and stem cell biologists. These models can be exploited for understanding complex pathophysiology and in cell-based drug screening. The UK also has strengths in molecular genetics, genomics and associated fields with significant recent investment in synthetic biology, including mammalian synthetic biology. Exploiting these core underpinning technologies for reading, writing and editing will enhance our understanding of brain tumours and developing sophisticated model systems.

The substantial investments recently committed to dementia research (including the Dementia Platform UK and the Dementia Research Institute) offer further opportunities for linking into outstanding tools and capability.

International linkages offer important avenues to develop partnerships and tackle the major challenges in the field of disease-related neuroscience – key examples include the Human Brain Project[5] and ERA-NET Neuron.

The MRC and the Brain Tumour Research charity will jointly develop a Workshop to bring the UK brain tumour and neurosciences research communities together to explore areas of common interests and opportunities for new research activities.

2.3. Diagnosis

Early and accurate diagnosis can transform survival and quality of life for people with a brain tumour. Survival for people diagnosed with a high-grade brain tumour through

emergency presentation is significantly worse than for those presenting through all other routes.[6] Early diagnosis in children and teenagers can also improve quality of life including reduced cognitive deficits, hormonal problems and visual loss.[7, 8, 9]

Late diagnosis of brain tumours is common. In adults and children respectively, 53% and 58% of high-grade brain tumours were diagnosed as an emergency in 2013 – more than any other cancer.[6] Therefore it is vital, where possible, to achieve early diagnosis to avoid first presentation as an emergency.

There are two broad research approaches towards achieving early diagnosis: the first involves laboratory science to discover and develop new and better detection technologies; and the second involves health services research to speed up patient routes to diagnosis.

2.3.1. Detection technologies

With the relatively high-risk associated with taking brain tumour biopsies, there is a real need to develop minimally invasive ways to diagnose brain tumours and monitor treatment. Imaging remains the primary method of brain tumour detection. As our understanding of the diversity of brain tumours increases, and with it the potential for greater tailoring of treatment to the distinct characteristics of a given tumour, the role of imaging as a diagnostic will become even more important. New or improved techniques have also the potential to monitor treatment response and provide novel end points for innovative trials.

Other opportunities exist to incorporate other minimally invasive technologies into the diagnosis of brain tumours, (although their use may also be extended to molecular stratification of patients and the monitoring of treatment). These include tumour-associated circulating biomarkers (such as circulating free DNA, circulating tumour cells, extracellular vesicles and metabolites) from bodily fluids (such as blood, urine or cerebrospinal fluid), and clinical spectroscopy. Understanding whether any of these methodologies has clinical utility in the diagnosis of brain tumours is thus a priority.

2.3.2. Routes to diagnosis

Brain tumours are difficult to diagnose because symptoms presented in isolation mimic other less serious conditions. As a rare disease, GPs will see few cases and may be unfamiliar with how an individual presents and there are cases of people with symptoms of a brain tumour being referred to optometrists.

The HeadSmart campaign aims to raise awareness of the signs and symptoms of brain tumours in children and teenagers amongst the general public and healthcare professionals.

The Brain Tumour Charity is funding research into the symptoms and factors associated with diagnostic delays in adults and, when this research is completed, will develop a campaign similar to HeadSmart.

Accurate diagnosis is also vital to ensure that people receive appropriate and effective treatment. Biomarkers (genes, molecules or biological substances) can be measured to predict response to treatments and match patients to relevant clinical trials. However, biomarker tests are not routine practice and access is varied.

Liquid biopsies enable diagnosis of type and grade of tumour without the need for invasive surgery, an approach already being pioneered in the United States. Without the risk of multiple surgeries, re-biopsies post-treatment for recurrent tumours are more attractive and open up new possibilities to investigate precision-targeted medicine. However, biomarkers are required to assess liquid biopsy samples and many UK centres do not have the resources or facilities in place to introduce this new technique.

2.4. Treatment

Effective treatment of brain tumours requires effective multi-disciplinary working. Standard of care begins with patients undergoing neurosurgery to obtain a diagnosis followed by radiotherapy and chemotherapy. Making the right treatment decisions for each patient requires expert input from neurosurgeons, neurologists, clinical and medical oncologists, nurse specialists, neuropathologists, and neuro-radiologists at every stage of the patient's cancer journey.

In children and young people, the team needs also to take the patient's stage of growth and development into account as well as the potential of the treatment to damage the developing brain and growing tissues.

In addition to the research opportunities that lie within individual treatment modalities (see below), there is huge potential to improve current treatments by optimising combinations and scheduling. A collaborative, team-based approach to clinical research also increases the quality of the research, the likelihood of a positive result and the scientific richness of the data.

2.4.1. Radiotherapy

Recent advances in technology and imaging have significantly increased the accuracy with which radiotherapy can be delivered to brain tumours. This has created exciting opportunities for research aimed at either reducing the side-effects of treatment by sparing critical structures within the healthy brain or increasing cure rates by escalating the dose delivered to the tumour. The UK is leading research aimed at improving tumour cure rates by combining radiotherapy with molecular targeted drugs, and investment in this area has potential to significantly increase the number of clinical trials available to patients as well as improving outcomes. For brain tumours in children and certain adult brain tumours, there is interest in evaluating the potential benefits of Proton Beam Therapy.

With the imminent opening of UK proton facilities at The Christie and University College Hospital, there is an opportunity to generate unique and highly informative data sets for

brain tumour patients. The expectation is that clinical data and outcomes will be recorded for all patients in terms of tumour control and for modelling normal tissue toxicity as a function of dose. Patient recorded outcome measures (PROMS) need to be refined and validated for these purposes. Unfortunately, the development of an electronic outcomes recording system is currently stalled; this has been highlighted to NHS England as a risk to the proton project. Participation in existing international clinical trials that allow protons is expected, and the UK community will develop and conduct world-leading randomised trials aimed at establishing the potential benefits of protons for selected brain tumour types. There is also scope for non-randomised studies aimed either at reducing toxicity or escalating treatment intensity.

2.4.2. Drugs

The fact that the healthy brain is protected by the blood-brain barrier (BBB) makes drug development for brain tumours extremely challenging. Furthermore, the high level of biological heterogeneity which characterises brain tumours (even those of the same type), makes it difficult for drug developers to identify single target molecules for treatment. To date, we have seen relatively few medicines in development which target brain penetration; despite multiple clinical trials resulting in 75 failed candidate medicines over 15 years,[(10)] currently only four drugs are licensed for primary brain tumours. Temozolomide is an example of a drug whose clinical and commercial success exemplifies the untapped potential and unmet need of brain tumour-specific drug development.

A different approach is to develop novel drug delivery systems that overcome the impact of the blood-brain barrier in achieving sustained effective drug concentration in the tumour tissue. There is significant research activity in this area in the UK.

The additional problem of treatment resistance makes drug development for high-grade glioma a major priority, and the distressingly poor survival rates for Diffuse Intrinsic Pontine Glioma identify this as another priority area. Co-ordinating research and clinical data across the age groups is likely to yield significant benefits. Also, due to the complexity of the disease and where in the body it manifests, drug discovery teams would benefit from establishing multi-disciplinary approaches to tackling this complexity. There are encouraging signs that this may be already happening with many laboratory-based, molecular researchers and also clinical researchers, using machine learning or artificial intelligence to increase their analytical and predictive potential.

High-quality discovery science is identifying new targets across the full range of brain tumour types and a streamlined approach to validating targets, and then developing active drugs that penetrate the CNS, is required.

Currently, the exploration of immunotherapies for brain tumours reflects a new strategy in addressing the tumour micro-environment and the host response, rather than targeting the tumour directly. This research is undertaken globally, but there is clear potential for the

UK to play a greater role in the development of immunomodulatory treatments for brain tumours, not least by promoting the establishment of clinical trials that patients in the UK may currently need to go abroad in order to join.

There is an opportunity for further research (translational neuroscience) on drug delivery to brain tumours.

2.4.3. Drug repurposing

The development of new drugs is a long and expensive process and failure rates are extremely high. New uses for medicines are frequently established over time, as science and experience guides the developer. Of the £100 billion spent annually by the global pharmaceutical industry, roughly 20% of that budget is directed towards developing new uses.[11] Recent evidence suggests that drugs developed for other conditions may also be useful for the treatment of cancer. The "process of identifying a new use for an existing drug in an indication outside the scope of the original indication" is referred to as drug repurposing[12] and was highlighted in the proposed Private Members' Off-patent Drugs Bill (2014). The Association of Medical Research Charities, alongside the Department of Health, has brokered a number of meetings with a wide range of stakeholders to address repurposing when sufficient evidence is available to support its use in a new indication.[13] The Drug Repurposing Group has published an independent report for organisations interested in this area setting out the routes that can be followed to achieve repurposing and the sources of information and advice available. [14] The report includes recommendations for further actions including how incentives to support repurposing might be developed.

2.4.4. Surgery

Neurosurgery is a fundamental driver and platform for brain tumour treatment and research. This is illustrated by an increasing number of sub-specialist brain tumour surgeons who are focused on improving clinical outcomes and this provides an opportunity for surgical-led research. To date, there has been relatively little investment in surgical studies but there is much to be gained by doing so. Surgery not only provides tissue to establish a histological diagnosis and enable a pipeline of laboratory and translational research but, as a treatment, it is increasingly evident that removing as much tumour as possible improves clinical outcomes - provided patients suffer no additional neurological injury. Indeed, the extent of resection independently conveys survival benefit and is synergistic with radiation and chemotherapy. Research opportunities are now arising from new technologies aimed at more accurately detecting tumour during surgery, defining the extent of resection, and the boundary with functioning brain. These technologies are not all widely available and continue to be developed and will need validation both as clinical adjuncts and research tools. These technologies include intra-operative imaging (MRI, Ultrasound, CT), optical visualisation of tumour (label and label-free fluorescence, confocal

microscopy), awake intra-operative mapping of brain function and real-time intra-operative molecular analysis of tissue (clinical spectroscopy, mass spectrometry).

Currently most research relies upon laboratory-based brain tumour models utilising tissue samples provided by the neurosurgeon but may not truly represent the real-life situation. New models are now being developed to address this. These now incorporate a surgical resection step to be more representative of the treatment the patient receives. Moreover, the emerging technologies above will give the surgeon the opportunity to study the "ultimate model" which is the live tumour in the live patient utilising real-time tumour identification and molecular profiling. This will identify new tumour biomarkers and areas for further research that could lead to novel treatments. They could also instantly inform the surgeon about the nature of the tumour and whether resection needs to be maximal or can be de-escalated. Eventually, of course, these technologies will support the marriage of robotics and automation into the surgical process.

Surgery, in addition to tumour resection, provides research opportunities in the application of other local therapies such as drug-eluting wafers or convection-enhanced delivery catheters, smart pumps, photodynamic therapy and nanotechnologies.

The role of the neurosurgeon, in managing the early patient pathway, means their engagement in early detection and diagnosis strategies will be essential.

There is, therefore, enormous scope to engage neurosurgeons more effectively in clinical and translational research. Pathologists and surgeons should work in partnership to simplify the consent and tissue acquisition process and maximise the quality and quantity of specimens in tissue banking initiatives. Neurosurgeons also have an essential role in clinical trials, evaluating new treatments by obtaining tissue specimens to demonstrate the extent to which drugs penetrate tumour cells and exert the desired biological effects, either as single agents or in combination with radiotherapy and/or chemotherapy. The feasibility and value of this approach has been demonstrated in UK studies that have successfully quantified penetration of radiation-sensitiser drugs into glioblastoma.

To develop more effective therapies for tumours that have recurred after initial treatment, we need to understand how the disease has changed over time. There is some evidence that re-resection has additional benefit, but to understand these changes requires neurosurgically-driven tumour-sampling strategies to collect material to support research and inform further treatment.

The Working Group agreed that it was important to engage more neurosurgeons in brain tumour research.

2.4.5. Clinical Trials

Due to the relatively small patient numbers for a given type of brain tumour, practice-changing trials need to be conducted across multiple countries and continents in order to recruit sufficient patients and/or incorporate innovative trial designs that maximise the use of data to generate clinically meaningful results in the context of small patient populations.

The UK has a strong track record of recruiting to paediatric brain tumour trials and approximately 50% of children are treated within trials. In contrast, only 5% of adults are recruited into brain tumour clinical trials. This is often attributed to a paucity of phase III trials. However, even when trials are available, many centres struggle to open. Research and Development (R&D) departments and trials units are sometimes reluctant to open studies that will only recruit small numbers.

In contrast, early phase clinical trials can be conducted in a much smaller number of centres and the UK is ideally positioned to lead this work. Recent research has recognised that in experimental medicine trials (where proof of principle and proof of concept are established), the UK is comparatively strong in Europe, running a close second with Germany as a site for trials. Within the brain tumour community, there is an effective network of eight adult neuro-oncology centres. The community is also part of the Innovative Therapies for Children with Cancer (ITCC) European network for early paediatric cancer drug development.[15] Participating centres have the infrastructure and enthusiasm required to participate in complex phase I-II trials that require neurosurgical, radiotherapeutic, pharmacological and radiological expertise (Appendix 5 sets out an example). Currently several UK researchers are leading such trials and there are particular strengths in the domain of radiotherapy-drug combinations in adult practice and targeted drug development in paediatric practice.

Targeted investment to support infrastructure across these networks would establish the UK as world-leading and would significantly increase the number of clinical trials available to patients with brain tumours.

It will be important to protect our ability to carry out clinical trials after our exit from the European Union.

The UK Clinical Trials Gateway[16] is a service that helps give people the confidence to join clinical trials by providing useful information about how trials work – while helping link them to researchers running trials they might be interested in.

The National Cancer Research Institute (NCRI) Brain Tumour Clinical Studies Group (CSG) has published a strategy document[17] outlining the current perspective and future challenges for brain tumour research in the UK. The CSG will use the 10 clinical areas defined by the James Lind Alliance Neuro-Oncology Priority Setting Partnership[18] (see section 2.6) as the foundation to develop new clinical trials for adults.

Several key steps to implement the new strategy have already been completed (eg re-organisation of the NCRI Brain Tumour CSG subgroups to be more disease-orientated) with new trials ideas already in development. The success of the strategy will be measured by: (i) the number of new trials on the portfolio; (ii) the number of patients participating in trials; and (iii) new chief investigators. Only by increasing the number of brain tumour trials on the portfolio can we increase access to research infrastructure at a local level (eg research nurses via the NIHR Clinical Research Network, R&D capacity) to make these trials available to more patients across more sites in the UK.

The NIHR reports that only 6.4% of brain tumour patients are participating in clinical studies compared to 13.3% for breast cancer and 61.4% for leukaemia. The low

percentage for brain tumour patients is explained principally by the current lack of interventions at a stage that is ready for clinical testing. However, in order to focus efforts, it may be helpful to have an ambition of 15% over the next five years.

2.5. Senior Research Leadership and Workforce

While there are clear pockets of excellence in UK brain tumour research, there remains a real need to develop and formalise senior leadership structures to co-ordinate local and national efforts. Boosting senior leadership in the UK would also create opportunities for junior researchers to gain a valuable breadth of knowledge and experience in the field – thereby sparking a much-needed uplift to the overall workforce in neuro-oncology. However, given the geographic spread of brain tumour expertise in the UK, a network-based approach to leadership that creates links within research themes rather than locations might prove more effective.

In paediatric neuro-oncology, the NCRI Children's Cancer and Leukaemia Clinical Studies Group has provided significant leadership in the clinical space, driving an encouraging uplift in the number of children on clinical trials, and has facilitated links with groups in Europe and North America.

In the adult clinical brain tumour community, the NCRI Brain Tumour Clinical Studies Group has provided leadership. Members represent the UK on the scientific committees of the relevant European and global societies and have formed strong links with researchers in the USA and Canada.

The recruitment to the UK of world-leading basic and translational researchers would further strengthen the adult brain tumour research community, although the last few years has shown an encouraging spark in the number of early-career researchers opting to focus their expertise on brain tumour research. Ensuring that these 'rising stars' are retained in the field must be a priority.

The limited workforce has also been cited as a specific barrier to clinical brain tumour research in the UK – limiting the repertoire of innovative clinical trials being led by UK researchers. A report recently written by the NCRI's Brain Tumour Clinical Studies Group singled out a number of issues including research capacity in a number of clinical disciplines, particularly pathology, radiology and medical oncology (the report claims that the UK is the only major European country with no medical oncologists specialising in brain tumours).

An effective way of growing research capacity and capability at all career stages, including senior research leadership, is to establish dedicated brain tumour research centres. Brain Tumour Research and The Brain Tumour Charity are already funding such centres. CRUK has released a call for applications for up to two large centres.

2.6. Living with, and beyond, a brain tumour:

The diagnosis of a brain tumour will have implications on long-term quality of life for many of those affected.[19] For thousands of people a brain tumour is a part of living, an aspect of their present and future. Unlike tumours in other areas of the body, brain tumours affect the characteristics and faculties that make people individuals. It affects the part of you that makes you 'who you are', and change may be radical and permanent.

Brain tumours are the biggest cancer killer of children. But thousands of children and young people face a difficult present and an uncertain future.[20] Many will live through childhood and into adulthood with the burden of the symptoms of their tumour and/or treatment. The impact on quality of life of the parents and carers must also not be forgotten.

It is critical that research into brain tumours has a focus on quality of life so that, after the completion of primary treatment, more people affected have a life to return to.

The James Lind Alliance (JLA) Priority Setting Partnerships agree research priorities that are of importance to patients and clinicians nationally and internationally. The JLA in Neuro-Oncology PSP developed the top 10 important questions for clinical research as agreed by the neuro-oncology community[21] (see Appendix 5). Some of these are areas particularly important for living with, and beyond, a brain tumour, including the long-term physical and cognitive effects of surgery and/or radiotherapy when treating people with a brain tumour. These should be embraced by the research community and funders.

There are clear opportunities here for clinical research and should be taken forward through a collaboration with the NCRI and the NIHR. The NCRI brain Clinical Studies Group Supportive & Palliative Care section are encouraging collaborative research on the JLA topics through “Incubator Days” supported by charity partners.

3. Barriers

3.1. Lack of pre-clinical models

Efficacy in laboratory tests has generally failed to translate into clinical benefit for brain tumour patients and the development of genuinely representative pre-clinical models is key to identifying and validating novel targeted therapies and re-purposed drugs (Sections 2.4.2 and 2.4.3) in a timely and informative manner. This encompasses both preliminary, high-throughput *in-vitro* screening of compounds and assessment of efficacy and safety of lead candidates in animal models.

PATIENT-DERIVED GLIOBLASTOMA MULTIFORME CULTURES

Although representative *in vivo* models remain the gold standard in pre-clinical testing, there is a significant role for glioblastoma multiforme (GBM) cell cultures in low-cost, high-throughput *in-vitro* assays. Historically, there has been an over-reliance on established cell lines that are easy to culture but which have lost the genetic profiles of the parent tumours which do not recapitulate the infiltrative behaviour of GBM when transplanted.

OPPORTUNITIES

Many patient-derived primary or short-term GBM cell lines are now available. Molecular characterisation of these cultures is critical to maximise their value both *in-vitro* and when establishing xenograft models.

There is emerging evidence that three-dimensional culture using spheroids and scaffolds more closely recapitulates glioma biology and treatment responses. Further development of 3-D models, including high-throughput screening assays, will reduce false positives at an early stage in drug development.

There is a specific need for representative, well-characterised *in-vitro* models of other primary brain tumours including low grade glioma (retaining IDH mutation), meningioma, paediatric tumours and brain metastases.

Brain tumour modelling in zebrafish (*Danio rerio*) is an emerging field with potential to bridge the gap between *in-vitro* and rodent models. Zebrafish models can be generated using gene-editing techniques or by xenotransplantation of human tumour cells. Orthotopic xenotransplantation is facilitated by the relatively large brain and the fact that the adaptive immune system does not mature in the embryos until approximately 28 days PF. Real-time bioimaging of human brain tumour cells expressing fluorescent or luciferase reporter genes and high-throughput screening approaches are feasible in this model.

RODENT MODELS OF GBM

Xenograft models, iehuman tumour cells grown as tumours in immuno-deficient mice, and syngeneic models ieartificially-generated mouse tumour cells implanted into immuno-competent mice, of GBM are widely available. Xenograft models that recapitulate key features of the human disease are widely available but require implantation in immuno-deficient mice. Syngeneic models use immuno-competent host mice and thus facilitate study of immunological phenomena, but are less representative. Genetically-engineered mouse models of glioma are available but to date have failed to recapitulate the genetic, molecular and morphological heterogeneity of the disease. There is enormous scope for research aimed at optimising animal models of brain tumours and this should be supported.

3.2. Lack of specific training/consultants with a specialist interest in neuro-oncology

For research opportunities to flourish, it is imperative that dedicated training for doctors involved in the diagnosis and treatment of brain tumours exists and that time is provided in consultant posts to allow research to be undertaken. A review of the current training of doctors involved in the care of brain tumour patients noted that training can be focused on producing generalist consultants with limited or no specified training in neuro-oncology. This is particularly true for medical oncology and, consequently, there is currently only one medical oncologist specialising in this field in the UK. This, in turn, leads to a gap in training opportunities due to a lack of specialist mentors.

New consultant posts dedicated to neuro-oncology (for example in the fields of medical oncology and neurology) need to be created. The creation of specialists in this field will create these much-needed opportunities for training, leading and inspiring more into the field of brain tumour research.

Royal Colleges currently not providing dedicated sub-specialism for neuro-oncology should consider sub-speciality training within their curricula.

NHS trusts should consider dedicated neuro-oncology consultant posts within the fields of neurosurgery, neurology, neuropathology, paediatrics, medical and clinical oncology.

3.3. Lack of co-operation and co-ordination

Collaboration is at the heart of the research endeavour - the sharing of knowledge, expertise and research ideas as well as the sharing of resources and infrastructure is essential to accelerate progress in research.

Co-ordination and co-operation are particularly important in brain tumour research because these are relatively rare cancers. Additionally, the research community itself is small and effective collaboration between multiple different health professions and

scientific disciplines, in both academia and industry, is required to ensure that scientific discoveries can be translated into clinical trials and then incorporated into treatment protocols. As highlighted elsewhere in this report, there are also opportunities to develop a more co-ordinated approach to the collection of high-quality brain tumour samples.

The Working Group acknowledged the enormous impact that effective co-ordination has had upon the quality and impact of research in the paediatric neuro-oncology field although much remains to be done. In contrast, investment in co-ordination and infrastructure for adult brain tumour research has been insufficient to deliver meaningful improvements and the collegiate approach found in paediatric neuro-oncology remains to be developed in adult neuro-oncology. The Working Group agreed that more co-ordination and co-operation is urgently needed.

The model of the NCRI Clinical Studies Groups[22], which co-ordinate the development of clinical research in specific cancer sites or areas, has proved effective where there is already an effective critical mass and existing research community. However, brain tumour research lags behind and more support will be needed. The NCRI's initiative to co-ordinate and build capacity and activity in radiotherapy and radiobiology research – in Clinical and Translational Radiotherapy Research (CTRad)[23] - provides an exemplar of where an underperforming area of research has been turned around by targeted significant investment to facilitate co-ordination. International collaboration is particularly important for rare tumours and additional mechanisms to support this are needed.

The brain tumour research community should come together to identify clear mechanisms to improve co-ordination and collaboration in the field. Where additional funding would be required to support this, the development of unified, bold, clear and costed proposals will enable funders to consider these and respond accordingly.

3.4. Accessing patient data for research

Due to the devastating impact on quality of life and survival from a brain tumour, people affected are highly motivated to share their health data for the purpose of research to accelerate development of new treatments and give *hope* to others who might be affected by the disease.

The media's response to initiatives such as care.data have been hostile and apprehensive. This has made it difficult for Government bodies to provide wider access to health data. People affected by a brain tumour understand this but are determined that their own data be made available on a much wider basis than national policy permits. In a 2017 survey by The Brain Tumour Charity of 270 people who have or have had a brain tumour, 97% wanted their data shared and 94% were happy to share information even if they could potentially be identified from it.[24] Appendix 7 sets out an example of the problem, plus an initiative to overcome the problems.

The registration of brain tumour data in England and Wales have been strengthened by the introduction of a national, population-based brain tumour registry within the National

Cancer Registration and Analysis Service (NCRAS), which uses improved and new data collection methods to capture more detailed, accurate and reliable data on brain and central nervous system (CNS) cases.

Despite this, the authors of *Achieving World-Class Cancer Outcomes: A strategy for England 2015-2020*[25] recognised that researchers and analysts have been unable to access data in a timely manner. This has directly impacted analysis of the diagnosis pathway in children and young people with a brain tumour through the HeadSmart campaign (Appendix A). The Brain Tumour Charity are developing an initiative to improve access to patient data for the benefit of patients and researchers (Appendix B). Regulators should respect the overwhelming wishes of patients for their data to be used in research. NHS Trusts and arms-length bodies need to ensure that there is greater awareness among people affected by a brain tumour about how their health data is used so as to ensure that individuals are less likely to opt-out of sharing data for purposes beyond their direct care.

Glossary

ABPI – Association of the British Pharmaceutical Industry

AMRC – Association of Medical Research Charities

Barts – Barts and The London School of Medicine and Dentistry, London, England

BBB – blood-brain barrier

BBSRC – Biotechnology and Biological Science Research Council

BIOMEDE – Biological Medicine for Diffuse Intrinsic Pontine Glioma Eradication

BRAIN UK – a virtual brain bank, a network of NHS and Academic Centres

BRC – Biomedical Research Centre funded by the NIHR

CBTRC – Children's Brain Tumour Research Centre

CCLG – Children's Cancer and Leukaemia Group, NCRI

Christie – The Christie Hospital, Manchester, England

CI – Cambridge Institute

CNS – central nervous system

CPRD – Clinical Practice Research Datalink

CRF – Clinical Research Facility funded by the NIHR

CRI – Clinical Research Infrastructure

Crick – The Francis Crick Institute, London, England

CRM – Centre for Regenerative Medicine

CRN – Clinical Research Network, funded by the NIHR

CRUK – Cancer Research UK

CT – computerised tomography

CTRad – Clinical and Translational Radiotherapy Research Working Group, NCRI

CTU – Clinical Trials Unit

DH – Department of Health, England (former name of the DHSC)

DHSC – Department of Health and Social Care, England (DH re-named January 2018)

DIPG – Diffuse Intrinsic Pontine Glioma

DNA – deoxyribonucleic acid

DOB – date of birth

ECMC – Experimental Cancer Medicine Centre

EGFR – estimated glomerular filtration rate

e-petition – electronic petition

EPSRC – Engineering and Physical Sciences Research Council

ERA – European Research Area

ESRC – Economic and Social Research Council

FFPE – formalin-fixed and paraffin-embedded (of pathology samples)

GBM – glioblastoma multiforme

GDPR – General Data Protection Regulation

GeL – Genomics England

gmbH – designation of a German company

GOSH – Great Ormond Street Hospital, London, England

GP – General Practitioner

HES – Hospital Episode Statistics

HRA – Health Regulation Authority

ICR – Institute of Cancer Research, England

IDH – isocitrate dehydrogenase

Imperial College – Imperial College, London, England

ITCC – Innovative Therapies for Children with Cancer

JLA – James Lind Alliance

JLAPSP – James Lind Alliance Priority Setting Partnerships

KCL – King's College London, England

LCRN – Local Clinical Research Network, funded by the NIHR

MHRA – Medicines and Healthcare products Regulatory Agency

MP – Member of Parliament

MRC – Medical Research Council

MRI – magnetic resonance imaging

MR-Linac – a combination of MRI scanner and linear accelerator technologies

MS – mass spectrometry

NCRAS – National Cancer Registration and Analysis Service

NCRI – National Cancer Research Institute

NHS – National Health Service

NIHR – National Institute for Health Research, funded by the DHSC

NMR – nuclear magnetic resonance

OIRO – Oxford Institute for Radiation Oncology

PEACE – Posthumous Evaluation of Advanced Cancer Environment

PET – positron emission tomography

PDGFRA – platelet-derived growth factor receptor A

PROMS – patient recorded outcome measures

PSP – (James Lind Alliance) Priority Setting Partnerships

PTEN – phosphatase and tensin homolog

RAF – Royal Air Force

R&D – Research and Development

SIOP CNS GCT II trial - A study looking at the treatment of intracranial germ cell tumours in children and young people

UCL – University College London, England

UCLH – University College London Hospital, England

UK – United Kingdom

UKCTG – UK Clinical Trials Gateway

US – United States (of America)

USA – United States of America

Wellcome – Wellcome Trust

3-D – three-dimensional

Appendices

Appendix 1 – Task and Finish Working Group on Brain Tumour Research

Terms of Reference

Background

The Minister for Life Sciences announced the formation of a Task and Finish Working Group at a House of Commons Debate on brain tumours on 18 April 2016. The Debate followed the report of the House of Commons Petitions Committee Inquiry into 'Funding into research for brain tumours', which was published on 14 March 2016. The Government's response to the report was published on 16 June 2016.

Terms of Reference

The Task and Finish Working Group on Brain Tumour Research will bring together clinicians, charities and officials to discuss how, working together with research funding partners, we can address the need to increase the level and impact of brain tumour research.

Taking into account evidence presented to the Committee, and the work of Cancer Research UK, the Working Group will:

1. Consider the barriers to brain tumour research, and how these might be overcome;
2. Consider the opportunities for brain tumour research and how these might be realised; and
3. Inform, and be informed by, the Department of Health's action plan on drug repurposing and the Government's wider activities to improve the R&D landscape – including issues around data sharing, etc.

The Task and Finish Working Group will:

a) Report to the Parliamentary Under Secretary of State for Public Health and Innovation;

b) Complete its tasks by September 2017 and submit a report to the Parliamentary Under Secretary of State for Public Health and Innovation;

c) Meet in person three times; and

d) Have a Secretariat provided by the Department of Health's Science, Research and Evidence Directorate.

Appendix 2 - Task and Finish Working Group on Brain Tumour Research

Membership

Name	Organisation	Role
Prof Chris Whitty (Chair)	Department of Health	Chief Scientific Adviser
Dr Virginia Acha	Association of the British Pharmaceutical Industry	Executive Director – Research, Medical & Innovation
Dr Helen Bodmer	Department for Business, Energy and Industrial Strategy	Head, MRC and BBSRC Team
Prof Anthony Chalmers	Institute of Cancer Sciences & Beatson West of Scotland Cancer Centre	Clinical Oncology
Sue Farrington Smith	Brain Tumour Research	Chief Executive
Dr Nick Goulden	Children with Cancer UK	Medical Research Director
Emma Greenwood	Cancer Research UK	Director of Policy
Dr Karen Kennedy	National Cancer Research Institute	Director
Dr Fiona McKevitt	Sheffield Teaching Hospitals NHS Foundation Trust	Consultant Neurologist. Chair of the Association of British Neurologists' Neuro-oncology Advisory Group
Dr Paul Mulholland	University College London Hospitals NHS Foundation Trust	Neuro-oncology (brain tumour unit)
Mr Kevin O'Neill	Imperial College Healthcare NHS Trust	Head of Neurosurgery
Prof Chris Harrison	NHS England	National Clinical Director for Cancer
Peter Realf		Patient Carer
Dr Nathan Richardson	Medical Research Council	Head of Molecular & Cellular Medicine
David Jenkinson	The Brain Tumour Charity	Chief Scientific Officer
Prof David Walker	University of Nottingham	Professor of Paediatric Oncology

Prof Tom Walley	NIHR Evaluation Trials and Studies	Director
Prof Tracy Warr	University of Wolverhampton	Professor of Neuro-oncology
Dr Louise Wood	Department of Health	Director of Science, Research & Evidence
Dr Helen Campbell	Secretariat	Portfolio Manager for Department of Health Cancer Research
Helen Bailey	Secretariat	Portfolio Administrator for Department of Health Cancer Research

Appendix 3 - Map of current UK brain tumour research activity

The data in the map at the end of this Appendix shows the annualised research spend on research into brain tumours. Data was collected from NCRI partners during the 2016 submission period and supplemented with data from Brain Tumour Research and the Brain Tumour Charity on the census date of 1 April 2016.

This funding supports a multitude of centres, units, programmes, projects, and individuals. The following is not complete but begins to map some of these research investments.

In paediatric neuro-oncology, the National Cancer Research Institute (NCRI) Children's Cancer and Leukaemia Clinical Studies Group has provided significant leadership in the clinical space, driving an encouraging uplift in the number of children on clinical trials, and has facilitated links with groups in Europe and North America. Professor Pam Kearns, Director of the CR UK Clinical Trials Unit, has also been credited with strengthening ties with international partners. In Cambridge, the recent recruitment of Professor Richard Gilbertson to the CRUK Cambridge Institute from St Jude's Hospital in the USA is likely to drive significant prioritisation of paediatric brain tumours within the Centre's strategy.

In the adult clinical brain tumour community, Anthony Chalmers, Susan Short and Colin Watts have led the NCRI Brain Clinical Studies Group and Novel Agents Sub-group for nearly 10 years. Moreover, they represent the UK on the scientific committees of the relevant European and global societies and have formed strong links with researchers in the USA and Canada. Brain Tumour Research have established four Centres of Excellence across the UK (led by Professor Geoff Pilkington at Portsmouth; Professor Oliver Hanemann at Plymouth; Professor Silvia Marino at Queen Mary University of London; and Dr Nelofer Syed and Mr Kevin O'Neill at Imperial College London), each representing opportunities to develop and strengthen existing leadership structures.

The last few years has shown an encouraging spark in the number of early-career researchers opting to focus their expertise on brain tumour research. Examples include Drs Steve Pollard, Paul Brennan, Dirk Sieger and Noor Gammoh (all in Edinburgh), Ross Carruthers (Glasgow) and Simona Parrinello (Imperial College London). Ensuring that these 'rising stars' are retained in the field must therefore be a priority.

Many organisations fund research into brain tumours. The following sets out some examples:

The Association of the British Pharmaceutical Industry (ABPI) represents innovative research-based biopharmaceutical companies, large, medium and small, leading an exciting new era of biosciences in the UK. Its industry, a major contributor to the economy of the UK, brings life-saving and life-enhancing medicines to patients. The Association represents companies who supply more than 80% of all branded medicines used by the

NHS and who are researching and developing the majority of the current medicines pipeline, ensuring that the UK remains at the forefront of helping patients prevent and overcome diseases. Its website is www.abpi.org.uk.

Brain Tumour Research currently funds four Centres of Research Excellence within the UK which serve to develop the research capacity of young career scientists. These form an effective working network which has catalysed the development of additional research programmes while underpinning key facilities including the support of BRAIN UK. Through its campaigning activities, Brain Tumour Research has strived to raise awareness of the need for greater investment into research into brain tumours in order to develop more effective treatments and ultimately a cure.

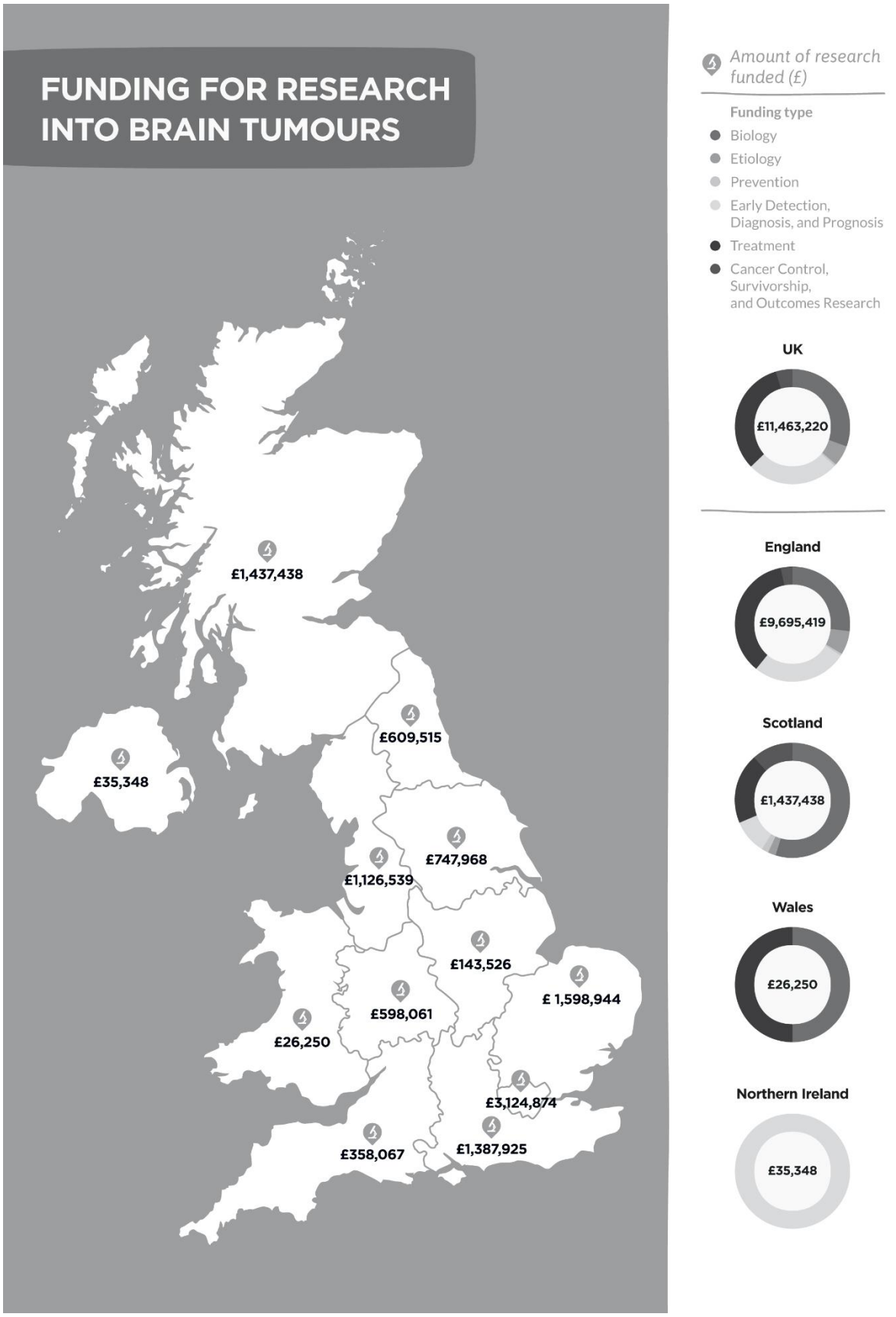
Cancer Research UK's aim is to spark long-term sustainable growth in the UK brain tumour research community which will drive progress for patients. To do this, the charity is investing in much-needed research infrastructure, funding the most innovative research, developing the next generation of brain tumour researchers, and is fostering multi-disciplinary collaborations within the UK and beyond. The charity already spends over £10m on brain tumour research, a figure that is set to be bolstered through an additional investment of £25m of ring-fenced funds over the next five years.

For over 100 years, the Medical Research Council has invested in research on behalf of the UK tax-payer to improve human health, produce skilled researchers, and advance and disseminate knowledge and technology to improve the quality of life and economic competitiveness of the UK and promote dialogue with the public about medical research. Its investments are driven by specialist independent expert review, focusing on the importance of the questions and needs in tackling human disease and the prospects for scientific progress. Cancer research is one of the major disease areas supported by the MRC.

The National Institute for Health Research (NIHR): improving the health and wealth of the nation through research. Established by the Department of Health, the NIHR:

- funds high quality research to improve health;
- trains and supports health researchers;
- provides world-class research facilities;
- works with the life sciences industry and charities to benefit all; and
- involves patients and the public at every step.

The Brain Tumour Charity are funding world-class research into brain tumours, from the earliest laboratory studies to clinical trials, and have an ambitious five-year strategy to halve the harm of brain tumours and double survival. The Brain Tumour Charity also fight brain tumours on many other fronts and raise awareness of the symptoms and effects of brain tumours to reduce diagnosis time. The Brain Tumour Charity makes a difference every day to the lives of people with a brain tumour and their families by providing free support and information services.


FUNDING FOR RESEARCH INTO BRAIN TUMOURS
£1,437,438
£609,515
£35,348
£747,968
£1,126,539
£143,526
£ 1,598,944
£598,061
£26,250
£3,124,874
£358,067
£1,387,925
Amount of research funded (£)
Funding type
Biology
Etiology
Prevention
Early Detection, Diagnosis, and Prognosis
Treatment
Cancer Control, Survivorship, and Outcomes Research
UK
£11,463,220
England
£9,695,419
Scotland
£1,437,438
Wales
£26,250
Northern Ireland
£35,348

Appendix 4 - Current major investments in UK research infrastructure

Funders of medical and health research in the UK such as the Medical Research Council, the Department of Health and Social Care's National Institute for Health Research, and Cancer Research UK, have major investments in research infrastructure. These investments provide under-pinning support for all types of medical and health research including brain tumour research.

Medical Research Council

The MRC supports research across the biomedical spectrum, from fundamental laboratory-based science to clinical trials, and in all major disease areas. Funding is delivered through a range of grants and personal awards to scientists in universities, medical schools and other research institutes, and through long-term strategic funding assigned to dedicated MRC Units and Institutes. MRC Units are strategic mission-focused initiatives, led and driven by an expert scientific director to promote novel, high-risk approaches, co-operative research programmes or the development of shared infrastructure and resources. Alongside performing ground-breaking research, they are also responsible for providing an excellent training environment to develop outstanding researchers with specialist and transferrable skills.

The MRC's main mechanism of support is through grants in response to projects submitted by independent investigators. This offers the most flexible and responsive approach to support the highest quality research, capitalising upon the developing knowledge and tools within the field. There are occasions when it is necessary to target investments in particular areas – eg bringing different disciplines together to tackle the big challenges and to improve infrastructure and specialist skills/capability that underpin crucial research. The MRC tends not to target these strategic investments at individual diseases. Rather, the MRC prefers to support cross-cutting areas that can deliver a much broader impact with limited resources across many diseases – eg stratified medicine, experimental medicine, regenerative medicine and support for cutting edge technologies.

Major MRC Unit/Institute investments relevant to brain tumour research

The MRC Cancer Unit at the University of Cambridge (core investment £4.8m pa): Research focuses on the mechanisms underlying the early stages of cancer development and progression, the development of new predictive markers and new methods for the discovery and early clinical development of small-molecule drugs.

The CRUK/MRC Oxford Institute for Radiation Oncology (core investment MRC £3.4m pa and CRUK £6.9m pa): The OIRO explores aspects of radiation biology that could yield new advances in the treatment of cancer, through understanding how cells respond to and repair radiation-induced DNA damage, defining the micro-environmental factors that affect these responses and identifying targets to alter tumour or normal tissue responses to radiation. Activities directly relevant to brain tumours are the D'Angiolella group (£1.8m) which is exploring the role of radio-sensitising agents in medulloblastoma and glioblastomas and the Sibson

Group (core-funded by CRUK) which has developed a powerful imaging agent for directing targeted irradiation of brain metastases.

The MRC Clinical Trial Unit (CTU), UCL (core investment £6.2m pa): The CTU carries out challenging and innovative clinical trials. It develops and implements methodological advances in study design, conduct and analysis to resolve internationally-important questions in infectious diseases and cancer.

The London Institute of Medical Sciences (core investment £17.8m pa): The focus of the LIMS is to explore the interface between genomics, physiology and epigenetics to gain a better understanding of metabolic diseases and how best to treat them, and use mechanistic studies to evaluate the impact of environmental stresses on gene regulation, expression and inheritance. Activity directly relevant to brain tumours is: a programme of work led by Simona Parinello (£3.2m) focused on understanding the cellular and molecular mechanisms underlying cancer of the nervous system.

The Francis Crick Institute (core MRC investment:£42m pa; a partnership investment involving CRUK, Wellcome, MRC, KCL, UCL and Imperial College). The Crick is a biomedical discovery institute established to understand the fundamental biology underlying health and disease. Work at the Crick aims to improve the understanding of disease progression and to develop novel approaches for the diagnosis, treatment and prevention of major illnesses including cancer. It brings together scientists from many disciplines within an outstanding research environment to help keep the UK at the forefront of medical research innovation. There are at the moment over 30 groups researching different aspects of cancer at the Crick, in subjects ranging from DNA damage and repair, tumour metabolism, and cell-signalling.

Other large-scale strategic infrastructure investments relevant to brain tumour research:

Unlocking research opportunities often requires broad-based investments that deliver value across a wide range of biological, technological and methodological platforms. Very often research investments in other cancer types, or other disease areas, will be informative to brain tumours. Whilst diseases of the brain do present some unique challenges (eg the blood-brain barrier and difficulties in taking biopsies), there are good examples where research, and associated infrastructure in broader areas, is hugely important, eg in applying innovative medical imaging technologies for diagnosis and in utilising new radiotherapy technologies for improved treatment-targeting.

Examples of recent cross-cutting strategic infrastructure investments that are important to brain tumour research include:

Clinical Research Infrastructure initiative

The MRC-led Clinical Research Infrastructure (CRI) initiative in 2014 to advance clinical research brought together £170m of funding from UK Government, devolved administrations, Arthritis Research UK, British Heart Foundation, the Wellcome Trust and Cancer Research UK. Twenty-three major investments were made, of which 15 employed and developed a range of next generation technologies to improve our understanding of cancer and improve diagnosis and treatment. Investment areas included:

- Developments in medical imaging (eg hyperpolarised MRI) to improve the identification and understanding of cancerous tissues;

- Technologies in single cell biology to enhance understanding of intra-tumour heterogeneity in cancer development and thus informing potential pathways to precision-targeted therapy;

- Investment of £24m in genomics and data analysis at Genomics England Ltd will help provide the infrastructure to interrogate the Government's 100,000 Genome project and thus advance research into the causes, consequences, prevention and treatment of diseases, including cancer (see also NIHR).

- Radiotherapy delivery systems (including MR-Linac) will help precisely locate tumours and adjust in real time the targets for radiation treatment, improving the accuracy of the treatment and minimising tissue damage.

These investments offer significant value to brain tumour research, offering new approaches to study tumours in situ, cancer genetics, cancer cell heterogeneity and metastasis. These developments will also support advances in precision medicine.

Molecular Pathology Hubs

Building on major MRC investments in stratified medicine, the MRC and EPSRC jointly invested £16m to support six molecular pathology nodes in 2015, led by the universities of Edinburgh, Glasgow, Leicester, Manchester, Newcastle and Nottingham. Each multi-disciplinary hub brings together researchers, clinicians and industry to develop molecular diagnostic tools to enable stratification in disease areas such as cancer. The Hubs will enhance the UK-wide capability to deliver cutting-edge molecular diagnostics, and enable clinicians to precisely target a treatment to maximise benefit for the patient.

Health and Biomedical informatics

Since 2012 the MRC has invested £100m in informatics infrastructure through the Farr Institute of Health Informatics Research and six major MRC Medical Bioinformatics Awards to enable a dramatic change in the use of large patient and research data sets. These investments have strengthened collaborative links (within academia and with industry and the NHS) and improved tools and infrastructure for researchers in the safe use of biological and patient data for medical research across all diseases. Many of the awards have significant relevance to cancer by facilitating the use, analysis and interpretation of large and diverse datasets related to cancer, such as disease risk factors, clinical research studies and genomics data. Research within the four Farr centres includes population research into childhood cancer, use of ecological data to generate hypotheses for brain and nervous system cancers, identification of cancer risks in children born via assisted conception, and risk factors associated with several cancers.

Building on the success of these initiatives, the MRC will lead on the establishment of a multi-funder UK institute for health and biomedical informatics research (Health Data Research UK). The MRC will invest a further £37.5m (plus £10m from partners) which represents a significant increase in strategic support for this area. The institute will be delivered in partnership; with the health research departments of England, Scotland and Wales, the Engineering and Physical Sciences Research Council (EPSRC), Economic and Social Research Council (ESRC), Wellcome Trust, and the British Heart Foundation. Other partnerships are also being explored.

Brain tissue banking

The MRC currently supports the UK-wide Brain Banks Network (£4.8m) comprising banks that have been set up around specific disorders and diseases, generally collecting post-mortem tissue. The MRC also funds two brain banks that focus on the collection of control tissue samples: the Sudden Death Brain and Tissue Bank at the University of Edinburgh; and the Thomas Willis Brain Collection at the Oxford Biomedical Research Centre. NCRI has also established the Confederation of Cancer Biobanks to promote harmonisation and co-ordination to maximise their use and impact.

MRC supports collections of brain tumour tissue through BRAIN UK which is a partner in the brain bank network and receives funding from Brain Tumour Research. BRAIN UK facilitates access to brain tumour samples for researchers from the archives of 26 of the NHS regional clinical neuroscience centres in the UK, effectively covering about 90% of the UK population.

UK Biobank

UK Biobank is a unique resource of 500,000 men and women aged 40-69 that supports the research into the influence of lifestyle, environment, genes and other factors on health and a wide range of diseases (including cancer). Prolonged follow-up of individuals through routine medical and other health-related records will allow the identification of comparatively large numbers of individuals who develop a wide range of conditions.

The MRC and the Wellcome Trust are the major funders of Biobank which has attracted £209m since its establishment in 2005. To date, the MRC has directly invested £92.5m which includes three enhancements, the most recent of which (2016-2022) is an investment of £9.3m for the imaging of 100,000 participants. This includes Brain MRI scans which could provide important insights into the prevention, diagnosis and treatment of brain tumours. Further investments from the British Heart Foundation, CRUK and NIHR, and with contributions from Diabetes UK, the Department of Health and the Scottish and Welsh governments, also support the core work of Biobank. Additional research project-based investments that exploit the Biobank resource answering targeted questions of health and disease are supported by a variety of funders.

Optical Microscopy

In 2013, the MRC, in partnership with BBSRC and EPSRC, invested £18m to enhance UK infrastructure in cutting-edge microscopy. These investments enabled researchers at KCL and the Universities of Cambridge, Dundee and Leeds to examine the properties and dynamics of molecules and cells in unprecedented detail, thus furthering our understanding of processes driving pathology, such as cancer, in living tissues.

MRC/NIHR Phenome Centre

See NIHR on following page.

National Institute for Health Research

The National Institute for Health Research (NIHR) was established in 2006 and funded by the Department of Health. It directs and co-ordinates translational research programmes for the National Health Service (NHS) in England. The NIHR provides research support and facilities in the NHS by funding different types of infrastructure investments, and those underpinning cancer and/or brain cancer research include:

NIHR Biomedical Research Centres (BRCs)

The NIHR funds Biomedical Research Centres (BRCs) within leading NHS and University partnerships to drive progress on innovation and translational research in biomedicine into NHS practice. These BRCs translate laboratory-based discoveries into new cutting-edge treatments, technologies, diagnostics and other interventions in clinical settings.

In September 2016, the Secretary of State for Health announced an £816m investment in 20 BRCs for five years from 2017. This funding includes the NIHR Royal Marsden/Institute of Cancer Research BRC (£45m) which will focus exclusively on cancer research. Five other BRCs will have dedicated cancer research themes. The funding amount for cancer research over five years across all BRCs is an estimated £131m.

NIHR Clinical Research Facilities (CRFs)

The NIHR funds Clinical Research Facilities (CRFs) for early translational (experimental medicine) research in the NHS. Clinical Research Facilities are dedicated purpose-built facilities that support world-class experimental medicine research to translate scientific advances into benefits for patients. NIHR funding meets the necessary recurrent NHS infrastructure costs of CRFs, such as clinical research nurses, technicians and Facility running costs. This funding gives patients access to brand new treatments, diagnostics and care. It is also crucial in helping us secure sustainable economic growth.

In December 2016, the Department of Health announced £112m investment in 23 NIHR CRFs for five years from 2017. It is estimated that approximately 30% of the research studies supported by these 23 NIHR CRFs are cancer studies.

NIHR/Cancer Research UK Experimental Cancer Medicine Centres (ECMCs)

Cancer Research UK (CRUK) and the UK Health Departments jointly fund the Experimental Cancer Medicine Centres (ECMCs). ECMCs are hubs where promising cancer treatments - including small molecule drugs, surgery, immunotherapy and vaccines - are safely tested for the first time in patients. ECMCs help give people with cancer access to cutting-edge treatments and precision medicine by testing new ways of detecting and monitoring the disease and how it responds to treatment.

In 2017, CRUK and the Departments of Health jointly invested a second phase of £36m over five years in 18 ECMCs for adult patients plus a network of Centres for children.

NIHR Clinical Research Network (NIHR CRN)

The NIHR Clinical Research Network (NIHR CRN) provides world-class health service infrastructure (eg research support staff, such as clinical research nurses, and research

support services, such as pharmacy, pathology and radiology) to support clinical research in the NHS in England. The NIHR CRN comprises 15 Local Clinical Research Networks (LCRNs) and a national Co-ordinating Centre, working together with shared principles values and behaviours. Each LCRN has a nominated local lead for cancer and all leaders come together to manage the national cancer research portfolio. The NIHR CRN has supported the delivery of over 2,500 cancer clinical research studies, including studies to improve treatments, quality of life and life expectancy.

The purpose of the NIHR CRN is to provide efficient and effective support for the initiation and delivery of funded research in the NHS. Some of this research is funded by the NIHR but most of it is funded by NHS non-commercial partners and industry. Department of Health & Social Care funding for the NIHR CRN is approximately £300m per year.

Genomics England

Genomics England (GeL) is a limited company established by DH launched by the Secretary of State for Health in 2013, which was set up to deliver the world-leading 100,000 Genomes Project. The Project covers patients suffering from rare diseases or cancer. Patients with 17 types of cancer are currently being recruited by NHS Genomic Medicine Centres, including those with adult brain tumours. The Project aims to enable more personalised treatment and faster access to clinical trials for patients with cancer as well as enabling cutting-edge research.

The 2015 Spending Review committed £250m NIHR funding to genomics and GeL. The Department of Health & Social Care is currently working with Ministers and delivery partners to develop the 2020 Vision for genomics in the context of the forthcoming Life Sciences Strategy.

NIHR Bioresource

The NIHR BioResource was launched in 2014 and provides a national cohort of healthy patients, their relatives and volunteers who are willing to provide clinical information and samples that will enable them to be recalled by genotype and phenotype for early translational (experimental medicine) research studies and early phase trials.

There are eight BioResource centres in England. They support collaborative research, including projects with the life sciences industry, to recruit participants for experimental medicine studies. These studies provide the potential to assess the molecular basis of disease, identify the most appropriate biomarkers for diagnosis and drug discovery, and test the mechanism of action and effects of new treatments. The NIHR BioResource aims to recruit 100k volunteers by 2017.

NIHR National Biosample Centre

The NIHR National Biosample Centre was launched in January 2015 to provide high throughput and high-quality biosample processing, storage and retrieval services to support NIHR-supported research and research funded by DH partners, such as publicly-funded research funders (eg MRC), charities (eg Wellcome, CRUK), as well as industry.

The NIHR National Biosample Centre repository takes a whole-system industrialised approach, applying engineering disciplines, to bring benefits for research through identifying efficiencies (eg easing access, improving start-up times and cost-savings),

managing risk, ensuring quality standards and protecting valuable samples and the information attached to them.

The Centre has the capacity to store up to 20 million samples and is a significant national health research resource. The NIHR National Biosample Centre was funded with a £24m capital grant from the Department of Health to the University of Oxford who worked in partnership with UK Biobank and UK Biocentre (UK Biobank's wholly-owned subsidiary) to design and deliver the Centre.

MRC/NIHR Phenome Centre

The MRC/NIHR Phenome Centre is a collaboration between Imperial College London and King's College London and works closely with NIHR's Biomedical Research Centres. It enables scientists to better understand and tackle diseases that are triggered by the environment as well as genetic causes, thereby increasing the potential to develop strategies for their prevention and treatment.

The Centre provides a service to researchers throughout the UK by offering fast, efficient and high-quality large-scale metabolic phenotyping of healthy and patient populations. This is achieved by using millions of pounds' worth of nuclear magnetic resonance (NMR) and mass spectrometry (MS) technology that give the most accurate readings to date of the exact chemical make-up of people's blood and urine. Phenotype data (and any other datasets available on samples) are analysed to identify biomarkers associated with disease-risk and environmental exposure, with the intent to drive healthcare solutions and improve patient care.

MRC and NIHR each allocated £5m (2013-2018). In addition, significant contributions from analytical technology companies, Waters Corporation (MS) and Bruker Biospin GmbH (NMR), have helped refine the technological platform for the assays and have helped also establish an international training facility which enables students, scientists and doctors from around the world to gain hands-on experience.

Cancer Research UK

CRUK is the largest single funder of all NCRI partners and its contribution to the total NCRI spend on brain tumour research has been increasing since 2011. Of the 10 institutions that receive more NCRI funding for brain tumour research, CRUK is the majority funder at those seven sites (source: NCRI, 2014).

CRUK Centres initiative

The CRUK Centres Network is one of the charity's top priority strategic initiatives and aims to support locations in delivering the highest quality translational research. Centres are partnerships working on a local level with Universities, NHS Hospital Trusts/Health Boards, cancer networks and other charities, and on a national level with Government and industry. Over the next five years, the Centres' initiative is expected to play a key role in delivering against CRUK's objectives in translational research. The aims of the initiative are to:

- Facilitate the delivery of translational research of the highest international quality;
- Facilitate multi-disciplinary collaboration, removing barriers between scientific disciplines and between discovery and clinical research;
- Build long lasting and effective partnerships, leveraging activities and funding of all partners;
- Accelerate progress in CRUK's strategic priorities through networks of excellence;
- Raise the profile of UK cancer research globally and attract international leaders, ensuring that its national network of excellence is visible on an international stage; and
- Train the clinical and non-clinical work force of the future.

Over the duration of the upcoming CRUK Centres funding period, the charity will be investing over £200m across the 13 locations that successfully achieved CRUK Centre/CRUK Major Centre status at the review held in October 2016. At present, four CRUK Centres have highlighted brain tumours as a focus area: these are Cambridge, Edinburgh, ICR and UCL.

Cambridge

At present there is a modest amount of CRUK-funded brain tumour activity in Cambridge – with the appointment (£7m over five years) of Richard Gilbertson as the Director of the Cambridge CRUK Cancer Centre a major addition. His expertise is in paediatric brain tumours, in particular the development of mouse models of medulloblastoma and ependymoma. This appointment is likely to drive significant prioritisation of brain tumour within the Centre's strategy, and it is likely that much of the Centre's activity in this disease will be built by and around the work of the Gilbertson group.

In addition to Richard Gilbertson, other CRUK-funded groups in Cambridge with a focus on brain tumours include:

- Colin Watts is developing a glioma-specific fluorescent dye that can guide surgery to maximise resection while minimising damage to healthy tissue, with a focus on adult glioma.
- Simon Tavare is utilising longitudinal samples and genomics approaches, along with the development of new statistical methods, to investigate the evolution of adult glioma. This work is being

undertaken in collaboration with Colin Watts. Professor Tavare is based at the core-funded CRUK Cambridge Institute (CRUK-CI).

- Kevin Brindle (also based at the CRUK-CI) is developing hyperpolarised 13C MRI to dissect the metabolic profiles of brain tumours. He also leads the CRUK-EPSRC Cancer Imaging Centre, jointly hosted with Manchester, which has a partial focus on brain tumours.

- James Nicholson is leading the SIOP CNS GCT II trial that is currently being run through the Birmingham Clinical Trials Unit. This is a prospective phase III trial for the diagnosis and treatment of paediatric intracranial germ cell tumours.

Edinburgh

The CRUK Centre in Edinburgh has stated that brain tumour research is one of its highest strategic priorities and has been focusing on this disease through one of its core research themes: Stem Cells and the Cancer Niche, which is led by Steve Pollard. He is based in the MRC-Centre for Regenerative Medicine (MRC-CRM) and was recruited to the Edinburgh Centre from UCL in 2013 as a CRUK Senior Research Fellow (over £2m over six years). His group is investigating the genes and pathways involved in neural stem cell identity, self-renewal and differentiation with the aim of translating this knowledge into new therapeutic targets. Paul Brennan is a Senior Clinical Lecturer specialising in neuro-oncology and translational neurosurgery. His focus is on translational research in glioma based on the stem cell-like cells thought to be responsible for these tumours – working in close collaboration with Steve Pollard. Brennan was also successful in his recent application for a CRUK Pioneer Award which will support his work into a novel method for drug delivery.

Beyond this research theme, Edinburgh has been actively building capacity in brain tumour through international recruitment:

- Dirk Sieger was recruited from the European Molecular Biology Laboratory in Heidelberg. He currently holds a CRUK Career Establishment Award (over £800k over six years) and is investigating the interactions between microglia and brain tumours using a larval zebrafish model system.

- Noor Gammoh was recruited from Memorial Sloan Kettering Cancer Centre. Her group is focused on autophagy, in particular the upstream processes that are essential for autophagosome formation and the impact of these processes on aggressive cancers such as glioblastoma. Dr Gammoh holds a CRUK Career Development Fellowship (over £1.6m over six years).

Edinburgh also leads on a brain tumour-focused CRUK Centres Network Accelerator Award (£3.7m). These awards provide infrastructure support to encourage collaboration between different organisations and boost ‘bench to bedside’ science. The project will support the development of open-access resources including patient-derived glioma stem cells, primary neural stem/progenitor cells, genome-edited cellular models, and an integrated database.

The Institute of Cancer Research (ICR)

Brain tumour research is singled out in the strategy for more general development however, with the ICR’s primary objective in this area to strengthen its links with the Royal Marsden’s brain tumour team. This has been achieved through Scheryll Alken, who is based jointly in this team and the ICR Drug Discovery Unit, acting as an interface between the two.

In terms of research within the Institute, there is a significant focus on paediatric brain tumours. Two groups are currently active in this area:

- Louis Chesler leads the Paediatric Solid Tumour Biology and Therapeutics team at the ICR. His group focuses on medulloblastoma, as well as neuroblastoma and rhabdomyosarcoma and is seeking to develop novel personalised approaches to paediatric cancer treatment.

- Chris Jones heads a team whose research aims to identify genes that drive the development of paediatric brain tumours, focusing on high-grade and Diffuse Intrinsic Pontine Glioma, and holds a CRUK Programme Award for this work. Due to the rarity of these tumours, sample access is facilitated through international collaborations. Dr Jones is the biology lead for the International Society for Paediatric Oncology European High-Grade Glioma Working Group.

University College London (UCL)

The CRUK Centre at UCL has highlighted brain tumours as a priority area and has been aiming to build capacity in this field. It is currently recruiting for the position of Chair in Radiation Oncology, with the intention that the role will link to the Proton Beam Therapy Centre to open at UCLH in 2018. This could be a highly significant appointment providing leadership in a field likely to rapidly advance in the UK over the coming year and it is expected that the Chair will be of an internationally-recognised calibre. UCL has three main brain tumour-specific objectives, highlighting its focus on training and networking in this disease:

- To develop a cross-centre brain tumour research programme and increase networking;
- To provide studentships dedicated to brain tumour research;
- To run neuro-oncology workshops with Barts, UCL and the Crick Institute to increase networking between these institutions and promote paediatric neuro-oncology research based at Great Ormond Street Hospital.

Additionally, UCL lead on the PEACE study (£4m), which is funded through a CRUK Centres Network Accelerator Award. The Award will support the collection of clinically-annotated post-mortem tissue and blood from patients, with either primary or secondary brain tumours, and the creation of a digital pathology hub. It will contribute to the study of tumour evolution, metastasis and resistance to treatment.

CRUK/NIHR Experimental Cancer Medicine Centres (ECMCs)

The Experimental Cancer Medicine Centre (ECMC) Network is a network of 18 adult and 11 paediatric 'virtual' centres across the UK designed to bring new treatments to cancer patients as quickly as possible. The network is a partnership between local NHS Trusts and universities enabling world-class health researchers and clinicians to work together to generate new approaches for beating cancer. The ECMCs are jointly supported by Cancer Research UK and the Departments of Health for England, Scotland, Wales and Northern Ireland providing a total of £36m over five years. Launched in 2006, the initiative is now in its third term of funding from 2017 to 2022.

Clinical Trials Units (CTUs)

CRUK supports the core infrastructure at eight UK Clinical Trials Units (CTUs) with a specific expertise in delivering cancer trials. CTUs deliver innovative and practice-changing clinical research that impacts the care and outcomes for cancer patients in the UK and across the world.

CTUs are specialist units with a specific remit to design, conduct, analyse and publish clinical trials and other well-designed studies. Trials may be early or late phase trials or population health-based studies. They provide expert statistical, epidemiological and other methodological advice. They centrally co-ordinate the delivery of multi-centre trials, and have robust systems to conduct and deliver clinical trials to the highest quality standards. CTUs are also responsible for ensuring that studies are conducted in compliance with the UK regulations governing the conduct of clinical trials and report to all the appropriate

agencies, including the Health Research Authority (HRA) and the Medicines and Healthcare products Regulatory Agency (MHRA).

CRUK funds eight CTUs that specialise in cancer clinical trials. Seven focus on a range of early and late phase clinical trials with clinical or biological endpoints and one CTU has a focus on large screening and population research-based studies.

Cancer Imaging Centres

Although not brain tumour-specific, the CRUK-EPSRC partnership has made significant investments in imaging through the Cancer Imaging Initiative: this entered into its second funding period in 2013. The Initiative supports four cancer imaging centres[26] which act as focal points of world-class clinical and pre-clinical research using a variety of techniques including optical microscopy, magnetic resonance imaging (MRI), functional MRI, ultrasound and positron emission tomography.

In terms of brain tumour-specific imaging research, Cambridge has significant capacity with both Kevin Brindle and Stephen Price's groups. Moreover, the University of Cambridge and the University of Manchester Imaging Centre includes brain tumours as a priority area. In Oxford, Nicola Sibson's group is at the forefront of research aimed at harnessing imaging modalities to improve the early detection of secondary brain tumours. While all three researchers are based at CRUK-funded Centres and Institutes, they also receive significant funding from other sources (the Wellcome Trust, NIHR and Medical Research Council respectively).

Appendix 5 – The BIOMEDE trial

BIOMEDE: BiOlogical MEDicines for DIPG Eradication; a randomised phase II trial of erlotinib, everolimus or dasatinib in combination with radiation therapy in newly diagnosed Diffuse Intrinsic Pontine Glioma

International Sponsor: Gustav Roussy, Paris, France

Chief Investigator: Jacques Grilles

UK National Co-ordinating Centre: Cancer Research UK Clinical Trials Unit, University of Birmingham, UK

Lead Investigator: Darren Hargrave, GOSH.

Diffuse Intrinsic Pontine Glioma (DIPG) is a universally fatal brain tumour occurring in childhood, diagnosed most frequently between five and seven years of age. Radiotherapy, the current standard treatment, is not curative and on average children survive only nine months from diagnosis. Recent DIPG research has identified expression of oncogenic pathways, for example EGFR overexpression, PTEN loss or PDGFRA amplification or mutation in 50%, 80%, and 20% of cases respectively. This has opened the possibility of effective targeted drug therapies for children with DIPG.

BIOMEDE is an international, investigator-led trial that introduces stereotactic biopsy to obtain diagnostic tissue for molecular screening to select patients for biomarker driven investigation of targeted drugs in a randomised phase II trial design. Access to the trial drugs (erlotinib, everolimus and dasatinib) is made possible through an academic-commercial partnership between two pharmaceutical companies and the European academic consortium, Innovative Therapies for Children with Cancer (ITCC: www.itcc-consortium.org).

The BIOMEDE trial is now open to recruitment internationally including in the UK (ClinicalTrials.gov identifier NCT02233049).

Appendix 6 – James Lind Alliance Priority Setting Partnership on neuro-oncology – Top 10 questions for research

The Top 10 research priorities were agreed in February 2015 as:

4. Do lifestyle factors (eg sleep, stress, diet) influence tumour growth in people with a brain or spinal cord tumour?
5. What is the effect on prognosis of interval scanning to detect tumour recurrence, compared with scanning on symptomatic recurrence, in people with a brain tumour?
6. Does earlier diagnosis improve outcomes, compared to standard diagnosis times, in people with a brain or spinal cord tumour?
7. In second recurrence glioblastoma, what is the effect of further treatment on survival and quality of life, compared with best supportive care?
8. Does earlier referral to specialist palliative care services at diagnosis improve quality of life and survival in people with a brain or spinal cord tumours?
9. Do molecular sub-typing techniques improve treatment selection, prediction and prognostication in people with a brain or spinal cord tumour?
10. What are the long-term physical and cognitive effects of surgery and/or radiotherapy when treating people with a brain or spinal cord tumour?
11. What is the effect of interventions to help carers cope with changes that occur in people with a brain or spinal cord tumour, compared with standard care?
12. What is the effect of additional strategies for managing fatigue, compared with standard care, in people with a brain or spinal cord tumour?
13. What is the effect of extent of resection on survival in people with suspected glioma of the brain or spinal cord?

Details at: http://neuro-oncology.org.uk/jla/

Appendix 7 – Accessing patient data for research

a) An example of the problems

HeadSmart is a UK-wide campaign to reduce diagnosis times of childhood brain tumours. In 2014, the Brain Tumour Charity in collaboration with the Children's Brain Tumour Research Centre (CBTRC) at the University of Nottingham funded a project seeking to assess the impact of the HeadSmart campaign on the referral practice across the primary: secondary care interface in the UK.

The HeadSmart team wanted to use subjects' date of birth (DOB) as a linkage[27] to ensure that the patient information across the datasets was referring to the same individuals with a brain tumour. This had not been an issue when similar research was undertaken in 2010-2013 to support the project linking data from the Clinical Practice Research Datalink (CPRD), National Cancer Registration and Analysis Service (NCRAS) and Hospital Episode Statistics (HES). Date of birth is a useful identifier but it is also crucial in order to calculate age when analysing data.

Whilst there is potential for data linkage across different data holders, there are unduly obstructive barriers to access health data. Health data is largely managed in silos with disparate, complex and opaque governance mechanisms and each repository may have a different access method.

Efforts by the HeadSmart team to get the data, specifically DOB, have been impeded due, in part, to the opacity of these processes and the linkage method could not be applied. The project has stalled at a substantial cost to The Brain Tumour Charity and the researcher has chosen to leave the research area of childhood brain tumours.

b) An example of an initiative to overcome the problems

The Brain Tumour Charity have identified three key ambitions from people affected by a brain tumour on the subject of health data: There is a desire to see health data about them utilised to its full potential; Secondly, people affected want to improve their understanding of quality of life to help them make tangible improvements to their own situations; and lastly, there is an appetite for more knowledge and awareness of non-prescribed treatments and alternative therapies.

In response to these three calls to actions, The Brain Tumour Charity are developing a patient-led global data bank, which will source existing NHS data and allow patients to unite in sharing their data, helping them to make better informed decisions about their own treatment plans, as well as helping vital research that could bring us closer to finding a cure.

The initiative will provide an invaluable platform where patients, clinicians and scientists can collaborate for better health outcomes.

Appendix 8 - Cancer Research UK's key areas for brain tumour research

Understand the biological basis for clinical trial outcomes, and drive a precision cancer medicine approach to managing brain tumours

Clinical trials for new brain tumour therapies are often based on limited pre-clinical data, they fail to appropriately select patients for molecularly targeted therapies and, in most cases, are predicated on a lack of understanding of whether the therapeutic will be pharmacologically-active in the tumour. Consequently, the majority of potential brain tumour therapies fail in early-phase clinical trials. In addition, there are few investigations into the biological basis for these failures.

There's a real need to develop novel approaches to understand how to monitor efficient delivery of treatment to the tumour, such as functional imaging, and to monitor treatment response and the development of resistance using minimally invasive approaches, such as circulating tumour DNA and circulating tumour cells. This research theme focuses on the need for more innovative, biologically-driven clinical trials that allow for the interrogation of individual responses to inform the underpinning biology of the disease.

Develop and use pre-clinical model systems that recapitulate human brain tumour biology and treatment approaches

Many clinical trials in brain tumours fail where the novel therapy has shown efficacy in the pre-clinical setting. This failure to translate is often due to the use of inaccurate brain tumour models and/or the failure to test novel therapies in the context of standard of care neurosurgery, radiotherapy and conventional chemotherapy.

There's a real need to build confidence in pre-clinical brain tumour studies and the evidence required to progress treatments to clinical trials. This includes the development and validation of pre-clinical brain tumour models, the use of functional imaging to test drug delivery and response, and setting a minimum standard for pre-clinical trial design that recapitulates the clinical setting in which novel treatments will be tested.

Identify and characterise new molecular drivers of brain tumours

Next generation sequencing and other '-omics' technologies have unmasked the heterogeneity of brain tumours and have revealed some drivers of disease formation and progression. However, to better understand molecular sub-types, there is a need to identify and functionally characterise novel molecular drivers of brain tumours including genomic, epigenetic or micro-environmental factors.

There's a real need to leverage the considerable '-omics' data available in brain tumours alongside cutting edge neural stem cell and pre-clinical models to identify novel brain tumour drivers that may guide patient stratification in clinical trials or serve as potential therapeutic targets.

Understand the role of the immune system in brain tumour biology and the development of immunotherapeutic strategies

The brain represents a unique immune environment in the body. Protected from the peripheral immune system by the blood-brain barrier, it boasts its own dedicated defence

system led by microglia – specialised immune cells tasked with preventing injury and inflammation. But very little is known about microglia and how they interact with developing tumours during disease evolution. Moreover, we now know that tumours disrupt the blood-brain barrier leading to an influx of circulating immune cells whose contribution to disease progression remains unclear. With immunotherapies now revolutionising treatments for many other types of solid tumours, understanding the immune landscape in brain tumours represents a real opportunity to develop similar approaches for people with brain tumours.

Understand the basis and clinical significance of brain tumour heterogeneity

While tumour heterogeneity has been shown to be a feature of brain tumours, we currently have a very incomplete picture of how it occurs, the extent to which it occurs and, crucially, its clinical significance This heterogeneity is likely to drive resistance to treatment and disease recurrence but the mechanisms driving heterogeneity and the contribution of treatment itself need to be explored in detail.

There's a real need to better understand the functional significance of brain tumour evolution and to consider how these insights might be used to design better treatment strategies.

Understand the pathophysiology of the blood-brain barrier (BBB) and its impact on treatment

Tasked with protecting the brain from toxins and other insults, the BBB actively blocks the movement of therapeutic agents and components of the peripheral immune system. But as tumours develop, interactions with the BBB lead to breaches in its integrity, although how this happens and how it affects the delivery of therapies is unknown.

There is a real need to characterise the structure, function and regulation of the BBB in brain tumours and build our understanding of how this differs among brain tumour sub-types. This improved understanding could lead to the development of improved delivery mechanisms for systemic treatments to brain tumours.

Understand the role of the tumour microenvironment in brain tumour development and progression

Insights from other tumour types have shown that the tumour micro-environment can significantly influence tumour behaviour. But there are real gaps in our knowledge about the cellular populations that comprise the unique brain tumour micro-environment and little understanding of how this ecosystem interacts with the tumour across space and time.

This theme is about understanding how the tumour micro-environment could be used as a basis for new treatment strategies for brain tumour patients.

Understand tumour initiation and progression within a developing brain

Studies aimed at surveying the molecular landscape of paediatric cancers have revealed a striking role for aberrations in neuro-developmental pathways, particularly epigenetic mechanisms regulating stem cell self-renewal. These findings have led to the hypothesis that paediatric brain tumours are, in essence, developmental disorders.

While this theory provides a useful conceptual framework to study these disorders, we are still a long way off from understanding how the molecular interface between neuro-development and tumorigenesis might be weaponised in innovative therapeutic strategies.

Develop and employ state-of-the-art molecular diagnostics for brain tumours

The current classification system for brain tumours is largely based on histology which fails to provide meaningful functional information about the tumour. There is a real opportunity to fully integrate the wealth of molecular pathology that has emerged from genomic studies into the diagnostic pipeline allowing for tumours to be classified into biologically meaningful sub-types according to their genetic, epigenetic and transcriptomic features.

A revamped classification system would improve stratification of patients into clinical trials and provide clinicians with upfront prognostic and/or predictive information to guide individualised treatment decisions.

Establish whether there are sub-types of paediatric brain tumours that respond to less intensive treatment

Treatment for paediatric brain tumours tends to be aggressive, often leaving children with debilitating side-effects which last into adulthood. There is a real opportunity to mine the wealth of genetic data from large-scale genomic, epigenetic and transcriptomic studies to identify the biological pathways that distinguish paediatric brain tumours that need to be treated aggressively from those that would respond well to gentler treatments. Pin-pointing the molecular hallmarks that define and govern aggressive tumour behaviour will enrich our understanding of disease pathogenesis, reveal new opportunities for therapeutic intervention and significantly improve the quality of life for many survivors.

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