Brain Tumour Initiative:

The Royal Marsden NHS Foundation Trust and
The Institute of Cancer Research supported by:

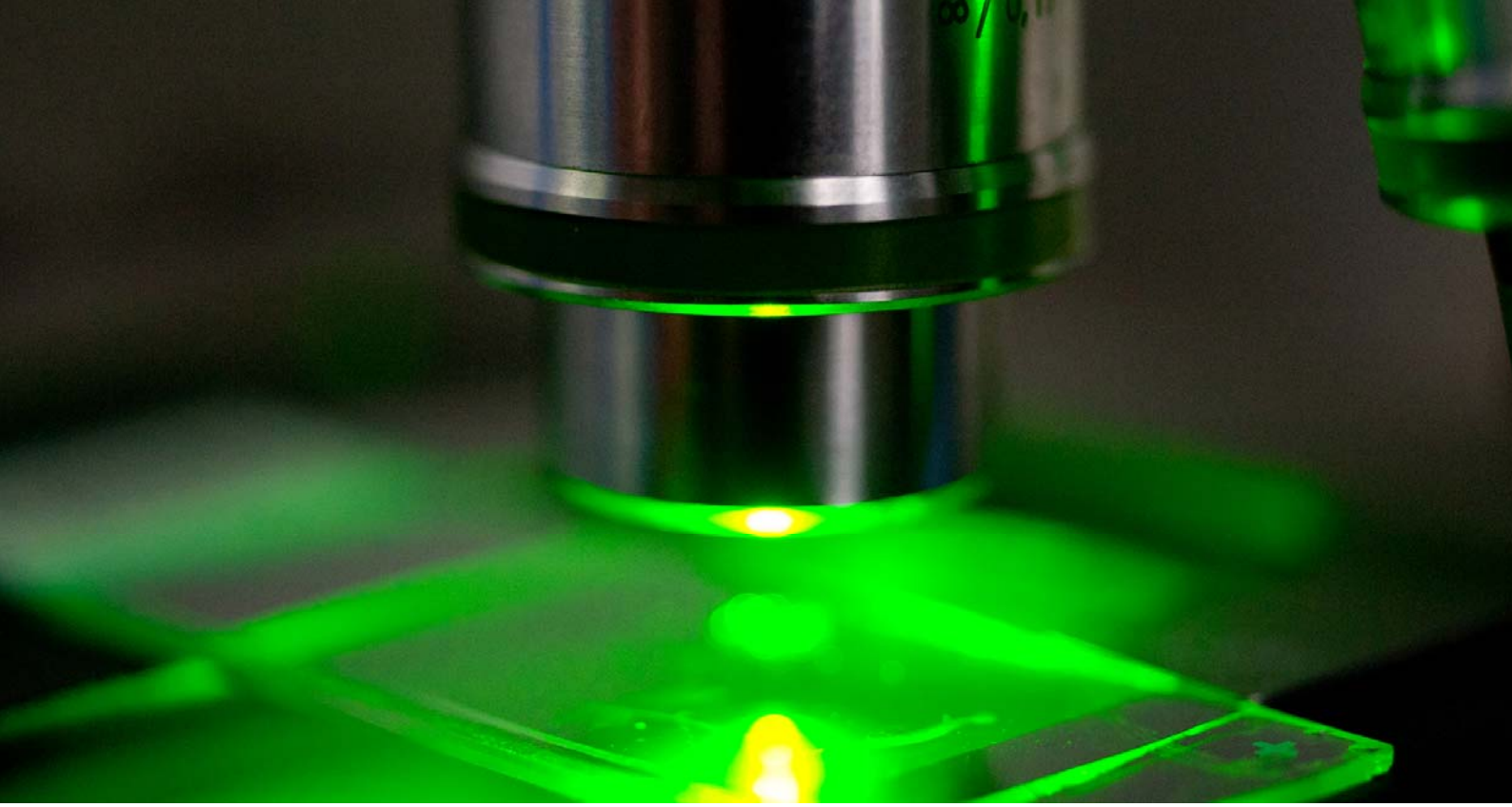
We remain extremely grateful to the Alison Fracella Research Trust for the support given to The Institute of Cancer Research (ICR) and the Royal Marsden Hospital (RMH) towards our Brain Tumour Initiative. Through a shared vision with the Alison Fracella Research Trust, we are aiming to make real advances in the treatment options available to glioblastoma patients. In this report we outline why the ICR and RMH is a unique environment in which to carry out this research and our progress so far, generously funded by the Trust.

Unique environment

The ICR together with its clinical partner the RMH comprise the largest Comprehensive Cancer Centre in Europe, employing over 3,300 scientific, clinical and nursing staff. The joint institution demonstrates breadth and depth in basic biomedical, translational and experimental cancer research, and provides a highly active and effective clinical research environment, with experienced internationally renowned academic clinicians and biomedical scientists (including 6 Fellows of the Royal Society, 16 FMedSci and 9 National Institute for Health Research Senior Investigators) engaged in leading-edge research. In November 2006, we were designated as the National Institute for Health Research (NIHR) Specialist Biomedical Research Centre for Cancer, with successful renewal in 2011.

The RMH is a specialist tertiary cancer centre based on two sites in London, and treats more than 40,000 cancer patients each year. It is the only NHS Trust in the UK to receive a rating of double excellent for both service quality and use of resources for 9 consecutive years in the assessment by the Healthcare Commission and the Care Quality Commission.

The ICR is a postgraduate College of the University of London, and has the highest percentage of research of any UK university assessed as 4* (world leading) in the areas of biological sciences and cancer studies in the most recent HEFCE Research Assessment Exercise (December 2008). The ICR was ranked as the UK's leading academic research centre by the Times Higher Education. The 2010 Higher Education Yearbook, produced by Evidence Ltd, reported that ICR's published research papers in biological science and clinical medicine had the greatest impact on our scientific peers of any Higher Education Institution or University in the UK.



Our approach to research emphasises close interaction between scientists and clinicians, with delivery of our research strategy through joint clinical / academic Divisions. This arrangement allows rapid and efficient flow between the laboratory and the clinic of research findings and ideas, patient samples (tumour, blood, etc), and scientific information and clinical data. The structure is fundamental to the success of our basic biomedical and experimental medicine research, and facilitates a very rapid transfer of innovation into pilot clinical studies, speeding up the delivery of scientific and clinical advances in diagnosis and treatment into real patient benefit.

This approach is reflected in our practice-changing advances in Radiotherapy, which have been made possible by physicists within our Joint Department of Physics, enabling rapid transfer of new technologies such as Intensity Modulated Radiotherapy (IMRT) through from the concept stage into pilot testing and validation, and then into large national randomised clinical trials, the results of which have now influenced NHS practice.

However, an area that perhaps best exemplifies our joint partnership is our world leading drug discovery team. We are very pleased to report that in April 2012, a multidisciplinary team from ICR and the RMH received a prestigious global award for their success in taking new cancer drugs from concept to patients.

This was the first time the Team Science Award, given by the American Association for Cancer Research (AACR), has been won outside the US. The AACR said its decision was based on “the tremendous impact this team has had in preclinical and clinical studies of cancer therapeutics”.

The Team members are from the Cancer Research UK Cancer Therapeutics Unit at the ICR, which discovers new drugs, and the Drug Development Unit at the ICR and RMH, which progresses drug candidates into clinical trials.

The AACR highlighted the team’s world-leading discovery of 16 innovative drug candidates over the past six years, and the progression of six of these drugs into Phase I clinical trials. The AACR also recognised the team’s work on the BRAF gene and its inhibitors and the discovery and development of abiraterone acetate. This new treatment for advanced prostate cancer, which is now licensed in the UK, Europe and the US, was an “outstanding example of

how a highly functioning translational team can rapidly translate a biologic hypothesis into a new cancer therapeutic."

"Overall, the work carried out by this multidisciplinary team over the last six years provides an outstanding example of the non-profit cancer drug discovery and development model that they have pioneered, as well as exemplifying a meritorious ability to collaborate productively with industry to accelerate patient benefit," the AACR Award citation said.

Award Team leader Professor Paul Workman, Director of the ICR's Cancer Research UK Cancer Therapeutics Unit, says: "The dedicated members of our multidisciplinary team are all individually experts in their respective fields of biology, pharmacology, chemistry and medical oncology. This expertise is really important – but it's also the very close collaboration between the scientists and doctors in our cancer research institute and partner hospital, as well as industry colleagues, that has really enhanced our ability to translate basic scientific research into new personalised cancer medicines.

"This award is a great endorsement of the academic drug discovery and development model that we pioneered. Most of all we are thrilled that we have been able to make a real and ongoing impact on the lives of cancer patients."

Some of the AACR Award winning team at the ICR/RMH

Glioblastoma Multiform: current treatment limitations, challenges and future directions

Glioblastoma Multiform (GBM) is the most common primary brain malignancy in adults. Under the umbrella of 'GBM' diagnosis lies a heterogeneous tumour group with particular molecular characteristics. Research has indicated that these tumours will not always respond to drugs in the same way and this may be due to these different genetic characteristics. Therefore, focus is shifting to the area of molecular research, analysing the genetic profile of these morphologically identical tumours, with different clinical behaviour and prognosis. Overall, prognosis of glioblastomas remains uniformly very poor and there are, as yet, many questions to be answered around the management of this challenging and dreadful disease, necessitating advances on all scientific and clinical fronts.

What have we achieved so far? Currently, the gold standard of care for patients with newly diagnosed glioblastoma is surgery followed by postoperative radiotherapy and chemotherapy with temozolomide. This knowledge derived from a referral Phase III clinical trial, the results of which have been published in the New England Journal of Medicine, and demonstrated that temozolomide can provide a significant clinical benefit over radiotherapy alone. However, the improvement in survival was modest; accounting 2.4 months and there is still a long way to go to improve the outlook of this disease.

But what makes this disease so challenging and difficult to manage effectively? Unfortunately, there is no easy answer to that question, as the disease is multifactoral and complex. Firstly, the brain possesses unique difficulties in the delivery of the treatment because of the existence of the blood brain barrier, which naturally prevents potential harmful agents from entering the brain. As a result this barrier limits the number of drugs which can actually pass through it and reach the tumour. Effective drugs need to have specific characteristics to penetrate the barrier and there is on-going research, aiming to identify these agents. At present we participate in a Phase I trial which recruits patients with recurrent glioblastoma, amenable to surgery. All patients participating in the trial receive the trial drug, for 4 days prior to their surgery. On the day of the operation, tumour samples are collected and extensive tests are conducted to investigate how much of the drug reaches the tumour and its effect on the tumour.

Secondly, brain tumours are unique compared to other cancers because of the very complex nature of the brain and the numerous functions that it performs. Consequently, patients are often taking many other types of drugs to control the disturbances of the brain which have been caused by the tumour. For example, anti-epileptics to control seizures, steroids to reduce the increased pressure and for inflammation in the brain, analgesics. These drugs may interact with the treatment regimens for the tumour, potentially reducing the effectiveness of these agents and complicating treatment.

Focusing on the nature of glioblastomas, as noted above, these tumours do not constitute a uniform clinical entity. This creates more challenges to the direction of understanding their pathogenesis. Furthermore, the hallmark of these tumours is their inherent tendency to recur, regardless of treatment. Despite improvement in neurosurgery, chemotherapy and radiotherapy, this hasn't changed significantly over the last 20 years. Defining the molecular biology of recurrence on glioblastomas is still poorly understood and current and future research focuses in this area.

What else have we achieved so far? Research carried out to form robust gene expression-based molecular classification of glioblastomas divides them into four subtypes: the Proneural, the Neural, the Classical, and Mesenchymal subtypes. Each subtype involves different patterns of somatic mutations and research demonstrated specific aberrations and gene expressions that define these subtypes. In detail, aberrations and gene expression of EGFR, defines the classical type, whereas NF1, and PDGFRA/IDH1 each define the Mesenchymal, and Proneural subtypes, respectively. Based on these features, tailored treatment for patients with glioblastoma multiform might change the outcome of the disease, given that research continues to investigate on targeted therapeutics.

Knowledge on the pathology and genetic profile of glioblastoma lead in identifying many genetic aberrations which are commonly found in GBM, a few examples of which are complete or partial gain of chromosome 7, loss or partial deletion of chromosome 10, *PTEN* mutations, amplification of *EGFR*, *CDKN2A* (p16) deletion and *TP53* mutation, etc. However, none of these genetic aberrations has so far been implemented as a diagnostic or prognostic marker in routine practice and more research is required.

Additionally, glioblastomas are known as highly vascular tumours that secrete several angiogenic factors. In fact they are among the most vascular of all malignancies as defined by Vascular Endotheliar Growth Factor (VEGF) content and microvascular density. Angiogenesis is the formation of new blood vessels in the tumour which are essential for the tumour growth and VEGF is a key regulator of this process, mediating endothelial cell proliferation and migration. Furthermore, VEGF is over-expressed in the majority of glioblastomas and the latter is associated with poorer prognosis. Research proved that the role of angiogenesis is pivotal in the biology of glioblastoma, indicating the rational to explore the role of angiogenic inhibitors in the treatment of this disease. Currently we participate in the AvaGlio Phase III trial, which is a European large Phase III study testing the role of bevacizumab, a VEGF inhibitor in the first line treatment for glioblastoma multiform. The study compares the standard temozolomide treatment of care for primary GBM with or without bevacizumab and the results will define the role of this angiogenic inhibitor in the front line treatment of glioblastomas. The area of angiogenesis inhibition is evolving and there are preclinical and clinical data demonstrating that inhibiting angiogenic pathways in glioblastoma leads to better outcomes.

Several studies are conducted in patients with GBM which are investigating different cell signalling pathways and chemicals and potential agents which can interfere with or modulate these pathways; these include exciting treatments such inhibitors of mTOR, protein kinase C, and platelet-derived growth factor. Unfortunately, results show a limited response to a single agent treatment; therefore research is moving on to the stage of second generation trials that combine two therapeutic agents. Combined treatment has specific requirements as researchers need to take into consideration the toxicity of treatment, the way these agents interact with each other and in the body, and practical considerations for the patients.

Research continues to investigate diagnostic and prognostic markers in glioblastomas. Additionally, on-going molecular biological trials could prove predictors of response to specific treatment based on the genetic profile of the disease. Our hope is that by throwing light upon individual biological alterations and better understanding of the disease and specific markers, we will be able to stratify patients with glioblastoma to the most effective targeted therapy.

Currently at The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust Hospital patients can be treated in the context of the following trials:

- A phase III study, investigating the role of bevacizumab in the first line treatment for patients with GBM
- The Phase I/II trial of BIBW 2992 and radiotherapy with or without temozolomide in patients newly diagnosed with GBM
- PARP inhibitor Phase I trial for patients with recurrent GBM
- Cediranib plus Gefitinib study (AstraZeneca/NCRI initiative-NCRI study) for patients with recurrent GBM
- National Brain Tumour (NBT) study investigating the genetic component of the disease
- The Phase I/IIa first time in human study investigatinfg the role of GSK2636771 (a PIK3- beta inhibitor) for patients with recurrent glioblastoma with PTEN deficiency.

We would like to extend our gratitude and thanks for the generous support of the Alison Fracella Research Trust, which enables us to translate hope into reality for patients with primary brain tumours.

Ioanna Fragkandrea – Profile

It is a pleasure to introduce myself as the researcher on brain tumours sponsored by the Alison Fracella Research Trust. My name is Dr Ioanna Fragkandrea and I am a Clinical Oncologist with a specific interest in the field of Neuro-oncology.

I qualified in 2006 from University of Ioanina (Greece) with distinctions in Medicine, and completed my post-graduate studies in Clinical Oncology, MSc with first class honours, at the Medical University of Athens, (Greece).

During my training I was awarded a scholarship at the University of Muenster (Germany), Department of Academic Radiotherapy, where I investigated the role of different radiotherapy techniques in several cancer types, fuelling my interest in cancer research. I am a member of a number of international bodies and member of the Hellenic Association of Clinical Oncologists that contributed to the development of treatment protocols in cancer patients. I am a founding member of two professional bodies, Hellenic Association of Head and Neck Cancer and Hellenic Association of Bone Metastasis. I have been engaged in epidemiological research in paediatric brain tumours and was proud to be part of the board developing the first national paediatric tumour data base in Greece.

Following completion of my specialty in Clinical Oncology, I was awarded a Scholarship from The Institute of Cancer Research at the Royal Marsden Hospital, UK, Department of Neuro-oncology and Lung Cancer, where I have been working for the last 2 years on combined modality treatments for brain and lung cancer patients.

In June 2012 I was delighted to be given the opportunity to join the Neuro-oncology research team, Department of Neuro-Oncology Unit at the Royal Marsden Hospital, UK, as a Clinical-Research Fellow running clinical trials in brain tumours, translating research into reality for brain cancer patients.

Whilst I have I gained a broad experience in the treatment of all cancer types, I have always had a specific interest in the epidemiology and treatment of brain tumours. Brain tumours, constitute an heterogenous and complex clinical entity, and we have a long way to go in the direction of gaining a better understanding of specific disease patterns and in order to identify more effective treatments.

Currently, The Institute of Cancer Research in association with the Neuro-oncology Unit at the Royal Marsden NHS Foundation Trust is involved in the development of targeted therapies for brain tumours. While in the era of targeted therapeutics, combination of more than one agents are investigated in the context of phase I/II innovative clinical trials, aiming to find better ways to fight this heterogenic disease.

The pioneering collaborative clinical trial with Cancer Research UK and the University of Glasgow, testing the role of olaparib (PARP-inhibitor) in recurrent glioblastoma has successfully been enrolling patients. This trial is first of its kind and we hope that in the near future we will be in the position to know if the investigational drug is successfully delivered to the tumour and targets inhibition by the use of biomarkers. We are in the process of opening an innovative phase I/IIa trial investigating the role of PIK3-beat inhibitors in patients with recurrent glioblastoma**.**

Our successful collaboration with pharmaceutical industry trials continues with multicentre trials of the National Cancer Research Institute (NCRI) Brain Tumour Group and the EORTC, testing new treatments in patients with newly diagnosed and recurrent glioblastoma and anaplastic gliomas.

Continuous translation between research and patients care is essential and part of my role as investigator on brain tumours is to build and secure sustainable bridge between them. I am determined that through this opportunity I can best support brain tumour research in the context of a reference hospital and a world known research institute that demand clinical excellence.

I passionately believe that it is essential to understand that despite the rarity of brain tumours, this entity does exist and needs to be equally prioritised in the policy-makers' agenda. We as clinicians need to focus on brain tumour research in order to improve our daily practices and care for our patients. The Brain Tumour Initiative and Alison Fracella Research Trust provides us the support needed to meet that criteria and continue our much needed joined efforts to the direction of more effective treatments for primary brain malignancies.

Dr Ioanna Fragkandrea

Dr Ioanna Fragkandrea - Clinical Research Fellow
E: ioanna.fragkandrea@rmh.nhs.uk

Dr Frank Saran - Consultant Clinical Oncologist, Head of Neuro-Oncology
Department of Neuro-Oncology and Paediatric Oncology
E: frank.saran@rmh.nhs.uk

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