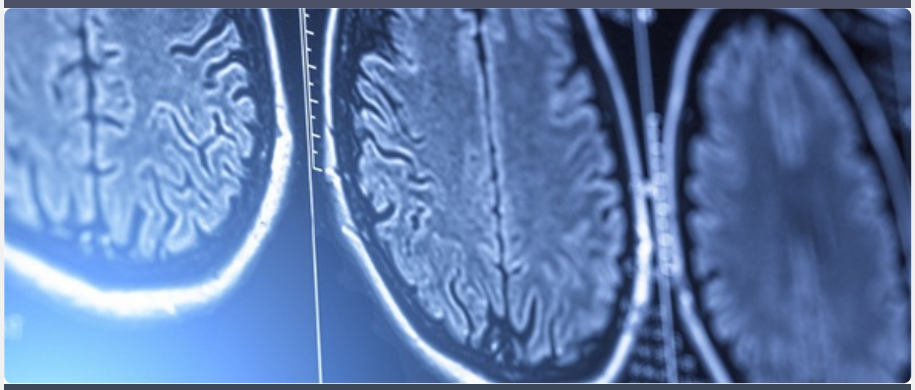
UNIVERSITY OF WOLVERHAMPTON

The Wolverhampton BRIEFING

Issue 1 Autumn 2020



Welcome to the first Wolverhampton Briefing. This new quarterly communication will provide an update on vital research taking place at the University of Wolverhampton.

Brain tumour research

Every year in the UK, around 9,700 new cases of primary brain tumours are diagnosed, including around 400 cases in children. Brain tumours have one of the lowest cancer survival rates – only 40 per cent of patients survive for one year following diagnosis, and more people under 40 years of age die of a brain tumour than any other cancer.

The efficacy of currently available treatments is hampered by the need to preserve normal brain function and by the tumours' intrinsic resistance to radiotherapy and conventional cytotoxic drugs. The incidence of brain tumour diagnosis is rising in the UK, not falling as other cancers are. There is an urgent need to develop new treatments based on a robust understanding of tumour biology.

At the University, along with charities and supporters, we have worked hard to increase income for this area of research, which has been historically severely underfunded, despite the low survival rate of patients. We have been partly successful, but the coronavirus pandemic is leading to a lower level of donations, a key income source.

Research objectives

Our brain tumour research programme at the University focusses around the development of novel therapies as well as identifying and repurposing drugs already used in the treatment of different cancers and other types of diseases (such as the anti-diabetes drug metformin).

In parallel, we are developing pre-clinical models of brain tumours that are more representative of the biology and behaviour of tumours in patients.

Dr Daniel Blakeway's PhD project
Glioblastoma is the most common and aggressive type of brain tumour in adults. In the UK, approximately 2,250 individuals are diagnosed with glioblastoma each year and the average survival is only 14 months after diagnosis, even with the best currently available treatment.

Glioblastoma is a complex disease and its diversity makes effective treatment very difficult, however this research project overcame the limitations of conventional drug resistance by targeting abnormal metabolic processes that are universally disregulated in these tumours whilst sparing normal cells and reducing negative side effects.

Tumours use much more glucose to generate energy than normal cells and high blood glucose levels have been associated with poor outcome in patients with glioblastoma.

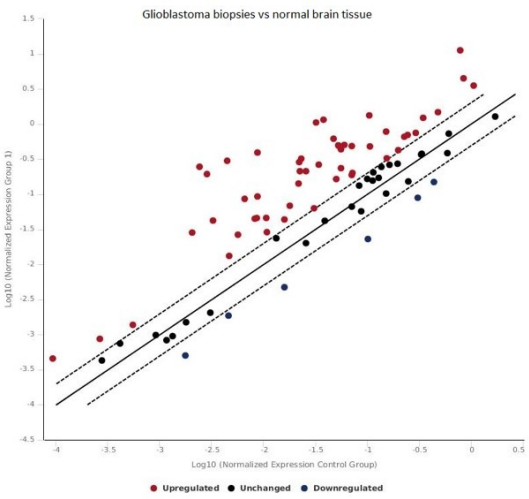
Similarly, reduced glucose intake and a high fat diet (the ketogenic diet) have been shown to significantly increase survival rates as glioblastoma cells are less able than normal cells to replace glucose with ketone bodies as an energy source. In addition, population studies have shown that diabetes patients treated with the anti-diabetic drug metformin have decreased risk of developing cancer.

In Daniel's PhD project, we aimed to investigate the therapeutic possibilities of disrupting glucose metabolism in glioblastoma cells by using a number of different approaches including:

- identifying potential new druggable targets in the glycolytic pathway
- investing molecular mechanisms associated with growth inhibition
- assessing synergy of metabolic therapies with existing treatment for glioblastoma.

Key findings

Hexokinase 2 (HK2) is a key enzyme that catalyses the start of glycolysis (the first step in the breakdown of glucose to extract energy for cellular metabolism).
• We proved that HK2 is an effective and viable therapeutic target that could benefit a significant proportion of glioblastoma patients.
• We demonstrated that inhibition of HK2 activity, through multiple mechanisms, including genetic knock-out, drugs and ketogenic diet, suppresses tumour cell growth and/or induces programmed cell death.
• We also evidenced that HK2 inhibition potentiates response to the most effective existing chemotherapy, temozolomide, although they have not yet validated an effective chemical inhibitor to induce synergy.



Graph shows upregulation of genes in the glucose metabolism pathway in glioblastoma compared to a normal brain (red dots are genes that are over-expressed in tumour tissue)

Next steps

In the next stage of the research, we

We are also establishing collaborations with medicinal chemist

will recapitulate the low carbohydrate ketogenic diet in their brain tumour cell model in order to determine whether they can induce the same molecular changes.

colleagues to try to develop a new drug to target the HK2 protein. Our ultimate aim is to develop effective medicinal and dietary therapeutic options for glioblastoma patients.

Impact

The Brain Tumour Research Team plays an important regional and national role in the under resourced brain tumour research sector, encouraging bright brains to the join the field, utilising funds from local and national charities to help advance the vital work and supporting donors with government lobbying.

Tracy Warr, professor in neuro-oncology

"Christopher Edwards recently joined the team on a PhD studentship to continue and build on Daniel's research on novel metabolic therapies for glioblastoma.

"It takes a long time for our research to be implemented into current clinical practice due to the intensity of initial identification and subsequent testing and validation . However, we are making great steps and this work needs to continue."

Peter Realf, father of Steven Realf

"We lost our son Steven. He was a trainee pilot in the RAF. Unfortunately, during his flying training he started having a few strange symptoms, pins and needles in his arms, nothing much. But it actually turned out to be a brain tumour. He had surgery but sadly died in August 2014.

"Funding is needed so that PhD students, like we have here (at the University of Wolverhampton), can continue the work they're doing. We need the brightest brains, the best brains, available to work on what's an incredibly complex issue."

The Brain Tumour Research team at the University of Wolverhampton would like to thank: The Colin Oliphant Charitable Trust, The Eveson Trust, The Rowlands Trust, The Michael Marsh Charitable Trust, The James Beattie Trust, The Adrian Pope Charitable Trust, The Harry Lance Memorial Fund, Balls to Cancer, Trudy's Trust, The Rotary Club of Wolverhampton, and donors to the University of Wolverhampton Giving Tuesday Campaign.

We are particularly grateful to the families and friends of over 20 individuals who have been affected by brain tumours, and the philanthropic donations that have been made in their memories.

If you would like to make a charitable donation to Brain Tumour Research at the University of Wolverhampton, please visit www.wlv.ac.uk/donate, or contact Terry Gibson, Development Manager, on 01902 32 1536 or t.gibson@wlv.ac.uk.

Get in contact

If you would like to get involved in research at the University of Wolverhampton, please email Adreen Hart-Rule, Media and Communications Manager:

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University of Wolverhampton Research

From pioneering research into brain tumours to seeking sustainable solutions, our research community's discoveries are having a positive impact on people around the world.

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