Brain Cancers in Ireland

Dr Brona Murphy is a senior lecturer in the Department of Physiology & Medical Physics and principal investigator within the Centre for Systems Medicine in the same department. The focus of Dr Murphy's research is to gain a better understanding of how brain tumours resist cell death upon treatment. Her group examines cell death pathways at the molecular level, in both adult and paediatric brain tumours, with the overall aim of increasing the susceptibility of these tumours to death. Dr Murphy hopes that by overcoming cell death resistance in these tumours, current and future therapies will be more effective, and ultimately patient survival will improve. Her research is funded by grants from the RCSI, HRB, SFI, NCRC and the H2020 Framework Programme.

Introduction

Brain tumours are the biggest cancer killer of children and adults under 40. Brain tumours reduce life expectancy by an average of 20 years, the highest of any cancer. Survival rates have improved little in over 40 years. The most common and aggressive primary brain tumour is glioblastoma (GBM). Despite intense effort to combat GBM with surgery, radiation and temozolomide (TMZ) chemotherapy, 90-95% of patients succumb to the disease within 5 years of diagnosis and nearly all patients experience disease recurrence, usually within 6-8 months of treatment onset. These stark facts require immediate action. New, better, more-targeted treatments are urgently required. To address this deficit, my research team and I, based in the Physiology Department at the Royal College of Surgeons in Ireland (RCSI) are currently examining the clinical applicability of cyclin-dependent kinase (CDK) inhibitors as a novel treatment option for GBM patients.

Cyclin-dependent kinase inhibitors (CKIs)

CDKs are critical regulatory enzymes that drive all cell cycle transitions. CDK-1, -2, -4, and -6, directly promote cell cycle progression, while CDKs, such as CDK-7, -8 and -9 regulate transcription. As one of the most fundamental traits of cancer cells involves their ability to sustain chronic proliferation, it is unsurprising that virtually all cancers, including GBM, harbor genomic alterations that lead to the constitutive activation of CDKs, resulting in unchecked cancer cell growth and division. Such observations have resulted in the expansion of translational research in the CDK inhibitor space, in particular for those tumors that are resistant to established treatments. Targeting the CDK4/6-Rb axis has proven the most successful approach in the clinic to date. The FDA has approved the CDK4/6 inhibitors, palbociclib, abemaciclib and ribociclib, as treatment for hormone receptor-positive metastatic breast cancer in combination with endocrine therapy. Preclinical studies using these CDK4/6 inhibitors in cell lines and animal models of GBM have also yielded positive results, however clinical trials undertaken to test these CKIs in glioma patients have not proven as successful. Several clinical trial are still ongoing however and results from same are eagerly awaited (NCT03158389, NCT02465060).

Research focus on CKIs

My group's interest in CDK inhibitors as a treatment for GBM patients has developed over the past number of years from comprehensive in vitro and in vivo research funded by the Health Research Board and Science Foundation Ireland. We have published that R-roscovitine, a first generation CDK inhibitor, down-regulates the anti-apoptotic protein, Mcl-1 in GBM, via its selective targeting by CDK9. Furthermore, we have shown that combining R-roscovitine with apoptosis-inducing agents, such as tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), re-establishes apoptotic sensitivity in both GBM cells grown as monolayers, in a stem-cell 3D tumour model and in a GBM patient neurosphere derived orthotopic mouse model. However, the dosing regimen required to maintain peak levels of R-roscovitine in the brain resulted in toxic side-effects that would preclude its widespread clinical utilisation, as is common for many such early CDK inhibitors.

Therefore, our further research was conducted with CYC065, a second-generation CDK inhibitor. CYC065 is mechanistically similar to R-roscovitine but with significantly improved potency (40-fold) and metabolic stability, giving it the propensity to be an even better therapeutic candidate. We have published that CYC065-treated neurospheres grown in vitro undergo significant levels of apoptosis. Importantly, we have also shown that GBM tumour-bearing animals treated by oral gavage with CYC065 showed no evidence of CYC065-induced toxicity and yet tumour growth was impeded. Additionally, as evidenced by Western Blot analysis of CYC065 targets in these tumours (RB, cyclin E and Mcl-1), there was strong evidence to suggest that CYC065 delivered by oral gavage successfully crossed the blood brain barrier. These extremely positive findings prompted us to more thoroughly examine CYC065's mechanism of action and also investigate a second CDK inhibitor, THZ1. THZ1 is a selective CDK7 inhibitor that ultimately leads to transcription inhibition and downregulation of short-lived mRNAs, such as Mcl-1 and has shown promise in recent preclinical studies as a potential treatment for GBM.

Current research projects

To further extend current knowledge surrounding the clinical potential of CKIs in the treatment of GBM patients we have recently utilised a panel of patient-derived gliomaspheres, provided by collaborators in Erasmus Medical Center, Rotterdam and the ICM (Brain & Spine Institute), Paris. These 3D models better recapitulate the physiological characteristics of patient tumors compared with the monolayer systems used in previous studies and are finalizing our results on CKIs' mechanism of action in GBM for publication.

This research work has also lead to our inclusion in the GLIOTRAIN initiative, which received €3.8 million in September 2017 from the European Commission's Horizon 2020 Marie Skłodowska-Curie Actions programme. The GLIOTRAIN consortium comprises 22 organisations across eight countries and includes leading academics, clinicians, private sector and not-for-profit partners across the fields of brain tumour biology, multi-omics, drug development, clinical research, bioinformatics, computational modelling and systems biology. GLIOTRAIN's aim is to identify and interrogate novel therapeutic strategies for application in GBM, while simultaneously implementing state of the art next generation sequencing to unravel disease resistance mechanisms.

Looking to the future

My research team and I are hopeful that our comprehensive preclinical assessment of CDK inhibition, will better inform future clinical application of CKIs in the GBM setting.