

Preface

According to the most recent figures, there are 650 newly diagnosed malignant brain tumours daily, severely threatening human health and quality of life. Almost 80% of these tumours are referred to as gliomas, a broad class of neuroectodermal tumours arising from the sustentacular neuroglial cells in the brain which includes astrocytomas, ependymomas and oligodendrogliomas. Of these gliomas, over 75% are astrocytomas which are classified as low-grade gliomas (LGGs, Grades I and II) or high-grade gliomas (HGGs, Grades III and IV). Grade IV astrocytoma is also known as glioblastoma (GBM) and is the most aggressive and lethal form of brain tumour which can be diagnosed. The first chapter of this book was written by Drs. Crilly and O'Halloran, who provide a structured overview of several of the major forms of brain tumours which arise in patients, including gliomas, along with clinically relevant targeted therapies which are currently under investigation. The authors discuss glioblastoma, oligodendroglioma, ependymoma and haemangioblastoma with regard to each of their mechanisms and pathways of resistance to currently used therapeutics. This extensive chapter provides a great introduction to the clinical and research challenges which arise in generating targeted therapies for a myriad of malignant brain tumours.

Several chapters of this book are focused on one particular type of glioma called glioblastoma (GBM). GBM is a highly invasive form of brain cancer with extremely poor prognostic outcome despite intensive treatment. Prognosis is reported as 'median survival' which, for adults with aggressive GBM treated with surgical resection, radiotherapy with concurrent and adjunct chemotherapy using the DNA alkylating agent, temozolomide (TMZ), is only 14.6 months. Notably, the absence of treatment typically yields a median survival rate of 3 months, and, despite treatment, the average 5-year survival rate for these patients remains at less than 5%. The effects of this form of cancer in terms of total years of life lost, over 20 years on average, in addition to the socioeconomic and financial impact of the intense treatment protocols required render GBM the most lethal form of brain tumour with the highest impact on the patient's quality of life post-diagnosis. Although genetic alterations significantly contribute to the pathology of GBM, including self-sufficiency in growth signals through receptor tyrosine kinase signalling,

insensitivity to antigrowth signals, evasion of apoptosis, angiogenesis, replicative potential and activation of invasive/metastatic pathways, the true epidemiology of GBM occurrence has not yet been fully elucidated. In this regard, researchers are attempting to develop gene therapy approaches in order to improve patient's outcome for both initial GBM diagnosis and recurrent tumour presentation. Due to its aggressive nature, several chapters of this book are focused on discussing the current status of novel targeted therapies for this form of brain tumour. For example, Dr. Tivnan outlines the role each of the adenosine triphosphate-binding cassette (ABC) superfamily multidrug resistance proteins may play in providing chemoresistance to GBM, reviewing all clinical trials which are currently targeting these proteins and the resistance mechanisms by which GBM cells have developed in order to maintain survival. The standard clinical protocol for GBM treatment is known as the Stupp protocol, a clinical regimen involving surgical resection and adjunct and concomitant chemotherapy in addition to radiotherapy. Drs. Shen and Hau discuss the mechanisms of resistance to targeted radiotherapy in this brain tumour underlining the role of the microenvironment, hypoxia and the *HIF-1* gene in this process. Identification of each of these elements has, to date, provided researchers with potential avenues through which alternate therapeutics may be developed in order to eliminate radiotherapy resistance.

As is the case for all diseases of the brain, the efficient delivery of potential therapeutics beyond the blood-brain barrier (BBB) is a major hindrance. Drs. Kealy and Campbell describe the normal physiology of the blood-brain barrier, its biological components and its compromised structure in GBM patients. They specify how the BBB affects targeted therapeutic administration and outline methods through which researchers are attempting to improve clinical outcome through BBB modifications during treatment.

The crossover of drug use among various forms of cancer is examined by Dr. O'Neill whereby the use of small molecules as targeted therapies in adult brain cancers, and their potential resistance in these diseases, can be assessed through their prior use in various other forms of cancer, for, example, TRAIL, EGFR and VEGFR inhibitors. The concept of 'lessons learnt from various cancer types' is further developed by Dr. Hill et al. discussing the repurposing of several drugs for brain tumour treatment, which are clinically successful for other cancer types, in an attempt to circumvent chemotherapy resistance. Following from the introduction of small molecule inhibitor use in brain tumours, Ms. Pokorny et al. examine the use of small molecule inhibitors specifically in GBM and how pathways of resistance occur and may be circumvented in this form of brain tumour.

Connor et al. review the topic of imaging targeted therapy response in GBM and how traditional imaging techniques such as computed tomography (CT), magnetic resonance imaging (MRI) and intraoperative ultrasound were routinely used to monitor the therapeutic effects of cancer interventions. They mention how there are now many additional non-invasive imaging modalities available, each with unique advantages, disadvantages and applications. The authors highlight that, despite advances made in non-invasive imaging techniques for brain tumour assessment, there remains a lack of effective imaging modalities which allow visualisation of

conversion of a proliferative to an invasive glioma phenotype particularly after treatment with targeted therapeutics such as anti-angiogenic or anti-invasive drugs. In this book, Smith et al. contribute the last of the malignant primary brain tumour chapters, reviewing the physiology, prevalence and treatment of a rare form of malignant brain cancer called meningioma. These brain tumours are typically benign; however, those that require targeted therapies quite often display resistance patterns similar to aggressive gliomas, and, as considered by Smith et al., several genetic alterations have been identified which may contribute to this resistance. The penultimate chapter was contributed by Dr. Zakaria, in which the potential role, if any, that targeted therapies have had on low-grade glioma progression-free survival (PFS) and overall survival (OS) rates and the cognitive decline which is quite often noted in these patients during treatment regimens, is reviewed. The author of this chapter comments that they must realise that low-grade gliomas will recur despite surgical intervention and become more aggressive and resistant to treatment; hence, there will always be an urgent need for new active targeted therapeutic agents, and resistance to such will be a constant challenge.

The final chapter of this book details a much more prevalent form of brain tumour, a secondary or metastatic brain tumour. Drs. Langley and Fidler estimate that approximately 200,000 cases of brain metastases occur in the United States each year and between 20 % and 40 % of patients with disseminated cancers will develop brain metastases during the course of their disease, most frequently arising from tumours that originate in the lung (40–50 %), breast (15–20 %) and skin (5–10 %). The authors comment on the mechanism of establishment and the role which the host interactions may play in contributing to the development of metastatic brain tumours, drawing attention to this potential target for reducing acquired resistance in metastatic brain tumours.

Overall, this book provides a historical study overview detailing the current treatment options available to brain tumour patients; the identification of genetic alterations in several glioma types, especially glioblastoma; and the development of targeted therapy to circumvent chemoresistance and the inherent resistance to these newer therapeutic approaches. The chapters in this book provide an extensive point of reference for up-to-date research and clinical applications of a myriad of treatment regimens for various brain tumour types.

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