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RACP Foundation Research Awards

FINAL REPORT

Project Title		Factors predisposing to post-operative epilepsy in patients with supratentorial gliomas
Name		Andrew Neal
Award Received		2017 Miriam Greenfield RACP Research Establishment Fellowship
Report Date		24 February 2018
Chief Investigator / Supervisor		Prof Terence O'Brien
Administering Institution		The University of Melbourne
Funding Period	Start Date:	12 January 2017
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PROJECT SUMMARY

Seizures are common in patients with brain tumours and up to one third of patients have seizures which are difficult to control with currently available medications. Despite this, unfortunately, most patients with brain tumours are excluded from epilepsy clinical trials.

Brain tumours are associated with increased levels of glutamate (a chemical involved with electrical activity) which increases the risk of seizures. A new anti-epileptic medication, called perampanel blocks the glutamate pathway and is a promising treatment. By targeting this molecular mechanism, it is believed that perampanel will control seizures better than other anti-epileptic drugs, and even prevent the occurrence of seizures.

As chief investigator, I am coordinating two randomised controlled trials examining the role of perampanel in brain tumours. The trial is recruiting participants with primary brain tumours who are planned to undergo brain tumour surgery.

Before the operation, brain glutamate levels within and around the tumour will be "mapped" using state-of-the-art 7T MRI at Melbourne University, in collaboration with the University of Pennsylvania in Philadelphia, USA. After the operation participants will be randomly assigned to either perampanel or standard epilepsy treatment.

These trials have been opened at major Melbourne hospitals.

It is hoped that findings from this trial can change the management of those with brain tumour associated seizures and help improve the quality of life for those with brain cancer.

Results from this fellowship project have already revealed that brain glutamate levels mapped with 7T MRI are linked to seizures and tumour aggressiveness. This will be the first study in the world to investigate the use of ultra-high field MRI to predict treatment response for epilepsy caused by brain tumours.

PROJECT AIMS / OBJECTIVES

Aim:

To examine molecular factors associated with post-operative glioma associated epilepsy

Objectives:

1. To develop a novel 7T MRI protocol for in-vivo quantification of tumour and peritumoural glutamate
2. To design and commence a clinical trial which explores the role of perampanel in the control and prevention of post-operative glioma associated seizures

SIGNIFICANCE AND OUTCOMES

Objective 1:

Increased tumour GluCEST was associated with features of more aggressive diffuse gliomas. GluCEST signal in the peritumoural region positively correlated with glioma associated seizures. I distinguished unique GluCEST contrast patterns, with distinct clinical and radiological features.

I have shown that 7T GluCEST imaging of gliomas can produce high quality images with spatial resolution arguably superior to many existing molecular sequences. Together with the correlation with tumour aggressiveness, this novel sequence has the potential to complement existing advanced imaging techniques. However, given the ability to non-invasively visualise and quantify glutamate, our findings raise the prospect of 7T GluCEST also being used to select patients for individualised anti-tumour and anti-seizure therapies directed at the glutamate pathway.

Objective 2:

This project will be significant to current practice and research, both locally and internationally. This project aims to help move the glioma-associated epilepsy field closer towards to an era of individualised, directed pharmacotherapy. The planned outcomes will help guide real-world clinical practice with high-level evidence, inform future directions of research and ultimately improve the quality of life for patients with gliomas

This unique trial will be only the third randomised controlled trial (RCT) to date which will limit enrolment to gliomas alone and the only RCT to be conducted solely in WHO grade II-III gliomas. This study will therefore have the most specific glioma population studied thus far in an epilepsy clinical trial. This will also be the first monotherapy epilepsy RCT utilizing perampanel and has a design that can examine the anti-epileptogenic properties of perampanel. A positive study would support the safe early use of perampanel as monotherapy in glioma associated epilepsy and would lead to the planned a larger randomized phase III trial.

Future Research

As part of a proposed post-doctoral fellowship I will continue to lead the PEGASUS trial to completion. This trial will coordinate the collection and storage of molecular, tissue and imaging data which will be coupled with detailed prospectively collected clinical information. In addition to PEGASUS, future proposed research will utilise this collected data and aim to fulfil the following objectives i) to further explore the role of 7T MRI molecular imaging techniques in neuro-oncology and epilepsy and ii) to develop a prospective diffuse glioma database exploring molecular factors and long-term seizure outcome

PUBLICATIONS / PRESENTATIONS
Submitted journal article:
Glutamate imaging (GluCEST and MRS) in gliomas with 7T MRI
Presentations:
CURE Acquired Epileptogenesis symposium (invited speaker) – Tumour associated Epilepsy (Feb 2017)
Melbourne Epilepsy @ Melbourne Brain Centre 2017 (speaker from abstract)
Translational Neuroscience Meeting (Royal Melbourne Hospital 2017)
PhD (University of Melbourne)
Clinical and Molecular factors associated with glioma associated epilepsy (submitted Jan 2018)
PEGASUS Trial Initiation Meetings
Royal Melbourne Hospital, St Vincent's Hospital Melbourne, Austin Hospital