BRAIN WORK

RACS Foundation scholarship recipient Dr Andrew Gogos is continuing research started by a previous RACS scholar with some exciting new discoveries

Melbourne Neurosurgery Trainee Dr Andrew Gogos is conducting PhD research into the properties and behaviours of glioma stem cells as part of a research project to find novel therapies to treat lower grade glioma and Glioblastoma multiforme (GBM), the most common and lethal primary brain tumour.

Dr Gogos is undertaking his research at the Department of Surgery at the Royal Melbourne Hospital and the Walter and Eliza Hall Institute, through the University of Melbourne.

He has received support from the College for his research through the Paul Mackay Bolton Scholarship for Cancer Research (2013) and the RACS Foundation/Tour de Cure Scholarship (2014).

Dr Gogos said that although most GBM occur de novo, approximately 20 per cent develop from lower grade tumours which progress. GBM remains universally fatal with a median survival of around 14 months after diagnosis.

He said a possible explanation for the difficulty in treating glioma was the existence of a small population of cells with stem-like properties.

Using patient-donated tumours, Dr Gogos and colleagues selectively culture glioma stem cells in order to study the molecular signalling pathways that control their behaviour.

"The Hippo pathway is involved in embryogenesis and organ size control and is active in adult stem cells, but not in differentiated tissue, including most cells of the adult brain," he said.

"That pathway, and its major effector Yes-associated protein (YAP), have been noted to be dysregulated in multiple cancer types. Work conducted within the Morokoff laboratory by Dr Katherine Holland, a previous RACS scholar, and others demonstrated that the pathway is abnormally active in GBM. Hippo pathway dysregulation may be part of how cancer returns.

"In normal physiology, YAP signals cells to divide and proliferate. Once an organ reaches maturity signalling is switched off but it appears to be dysregulated in some cancers, including brain cancer.

"We are hoping that by finding a way to target glioma stems cells and the YAP signalling pathways that we may provide long awaited therapeutic advances for patients with glioma.

"We have already demonstrated that YAP protein and mRNA expression is higher in GBM than lower grade tumours and that high YAP expression was associated with much worse overall survival for patients with Grade II and III glioma."

Dr Gogos said a distinctive feature of his research was the ability to study and grow GBM in the laboratory using tumours donated by patients treated at the Royal Melbourne Hospital.

"We are one of the few research units conducting this type of work," he said.

"That is a great advantage because it allows us to work on the best possible model of the disease."

As part of his PhD, Dr Gogos is also developing a knockout model to further explore the function of YAP in glioma stem cells.

Using cutting-edge technology, and a new method called CRISPR/Cas9, Dr Gogos is appropriating a defence mechanism found in bacteria an archea to cause mutations in specific regions of the genome. Tumour cells are transfected with a fluorescently labelled Cas9 and specially designed guide that is specific to the YAP gene.

Once activated, the Cas9 causes a double stranded DNA break within the YAP gene.

"This is very exciting science and quite new," Dr Gogos said.

"The double strand break is repaired with errors, creating inactivating mutations within the YAP gene. It shows us what can be achieved by targeting the YAP protein with drugs.

"We already know that YAP is highly expressed in brain tumours but not in normal brain cells so it makes it a great target to investigate.

"We are hoping that if we can knock it out, the tumour cells will stop proliferating.

"The CRISPR method was first described only two years ago so it is very new and has never been used in brain tumour research or on this specific gene.

Dr Gogos said the research team was also now analysing existing drugs to see which might have the potential to inhibit YAP while also testing novel drug therapies in the laboratory.

He said that while it was too early to put a time frame on the development of new GBM therapies, researchers were confident that technologies like CRISPR/Cas9 could add to the understanding of disease progression and recurrence.

"Glioblastoma is such a terrible disease and it's hard to witness great strides being made in the treatment of other cancers when the prognosis for patients with GBM remains dismal," he said.

"Harvey Cushing, who is considered the father of neurosurgery, said nearly 100 years ago that GBM was not a surgical disease, meaning that surgeons could not cure it.

"Unfortunately, this remains true today which is why so many of us who treat these patients are so passionate about finding new therapies.

"Hopefully, the work we are now engaged in might open new avenues of treatment for GBM and other gliomas and while my work is laboratory based, it is a vital first step in advancing our understanding of the genetic drivers and cellular pathways of the disease. "

Dr Gogos is conducting his research under the supervision of Professor Tony Burgess, from the Walter and Eliza Hall Institute, neurosurgeons Mr Andrew Morokoff and Associate Professor Kate Drummond, and scientist Dr Hongjian Zhu.

A SET 4 Neurosurgery Trainee, he maintains a light clinical roster at the Royal Melbourne Hospital, attends theatre to collect tumour specimens and attends regular neuro-oncology meetings.

His work has also received support through a Brain Foundation Research Grant, a Royal Melbourne Hospital Victor Hurley Medical Research Grant and an NHMRC Postgraduate Scholarship.

A member of the College's Section of Academic Surgery, Dr Gogos said he was grateful for the support given by the RACS, particularly in the early years of his research career.

"This support from the RACS is crucial if Trainees are to take time away from their clinical work to conduct research," he said.

"It was a difficult decision to make, given the time required to become a Neurosurgical Fellow, but my goal is to become a surgeon-scientist.

"The work I have been doing provides great intellectual stimulation in a quickly evolving area. Understanding how these tumour stem cells work and how that knowledge could directly help very sick patients is of greatest interest to me."

The Paul Mackay Bolton Scholarship for Cancer Research was established by Harry Bolton in memory of his late son, Paul, a distinguished surgeon, teacher and researcher who died from colorectal cancer in 1978 aged 39. The scholarship is intended to support applicants who wish to take time away from clinical positions to undertake a full-time research project into the prevention, causes, effects, treatment and/or care of cancer.

The Foundation for Surgery Tour de Cure Cancer Research Scholarship was established in conjunction with the College to support Fellows, Trainees and International Medical Graduates wishing to undertake a cancer research project.

The Tour de Cure raises funds for cancer research through an annual bike ride. Next year, the ride will stretch from Brisbane to Sydney and Dr Gogos intends to participate as both a rider and medical support officer.

With Karen Murphy

CAREER HIGHLIGHTS

- **2015** NHMRC Postgraduate Scholarship
- **2014** Foundation for Surgery/Tour de cure Scholarship
- **2013** Neurological Society of Australia Research Scholarship
- **2013** Paul Mackay Bolton Scholarship for Cancer Research
- **2013** University of Melbourne Melville Hughes Scholarship

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