

Department of Neurosurgery

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The Department of Neurosurgery has active and laboratory brain research programs, which augment each of the clinical specialised programs undertaken by the department alone in conjunction with the Department of Neurology. The specialised clinical programs include Brain Tumours, Cerebrovascular, Spinal Disorders, Neuro-trauma, Pain Surgery, Neuro-endocrinology, Epilepsy and Functional Neurosurgery. The Department treats over 6000 outpatients each year and is involved in over 2200 operations annually at The Royal Melbourne Hospital.

Clinical Initiatives

The major recent clinical initiatives have involved the establishment of dedicated specialist neurosurgery outpatient clinics. The cerebrovascular clinic, led by Mr John Laidlaw treats patients with complex cerebrovascular disorders in conjunction with members of the Department of Neurology (Dr Bernard Yan) and neuroradiology (Professor Peter Mitchell).

A Neuro-oncology Clinic, established by Dr Kate Drummond is attended by members of the Department of Oncology including Professor Mark Rosenthal and Professor David Ashley. This clinic provides a holistic unified approach for the treatment of patients with malignant brain tumours. Patients with complex pain disorders are treated by Professor Peter Teddy in the Pain Clinic. This clinic is also attended by anaesthetists, rehabilitation specialists and social workers.

Dr Richard Bittar has been recruited to the Department and together with Professor Peter Teddy and Dr Andrew Evans from the Department of Neurology a specialised Movement Disorders Program was established treating patients with complex movement disorders such as occurs in Parkinson's Disease. This involves the insertion of deep brain stimulators into highly selected patients.



Research Overview

The Department of Neurosurgery's clinical and laboratory research activities augment each of the specialised clinical programs including Brain

Tumours, Cerebrovascular, Spinal Disorders, Neuro-trauma, Pain, Neuro-endocrinology, Epilepsy and Functional Neurosurgery.

The Department of Neurosurgery continues to be involved in a major collaborative Brain Tumour Research Program in conjunction with the Department of Surgery at The University of Melbourne, the Ludwig Institute for Cancer Research, the Walter and Eliza Hall Institute for Medical Research, the Howard Florey Research Institute and the Departments of Anatomy and Cell Biology of The University of Melbourne. This research program involves the study of molecular and cellular events that lead to the development of brain cancer and the complex intracellular signalling pathway, thereby leading to the development of novel biological controls.

In addition the Department of Neurosurgery in conjunction with members of the University's Department of Medicine is investigating the molecular events underlying the development of epilepsy and brain cancer. The laboratory research is undertaken almost exclusively within the Department of Surgery at The University of Melbourne. The laboratories are located within the Clinical Sciences Building, and are collocated with the Hospital.

In conjunction with the Department of Endocrinology and the Department of Ophthalmology the Department of Neurosurgery is undertaking the study of the use of optical coherence tomography in measuring the retinal nerve fibre layer and predicting the visual outcome following treatment for optic compressive pathology.

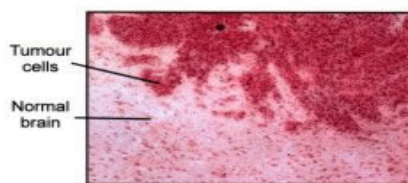
The Department of Neurosurgery is involved in a number of clinical research programs involving the optimal management of patients with severe brain

trauma. The Department also has a vigorous clinical research program studying the management of patients following subarachnoid haemorrhage from cerebral aneurysm.

Brain Tumours

Cancers arising primarily from the brain are the fourth most important type of cancer in terms of life years lost, because these tumours disproportionately affect young people. They are the most common type of cancer in children. In addition, one third of all deaths in our society are due to cancer, and in a quarter of those people dying from cancer the tumour will have spread to the brain.

In over 60% of patients with brain tumours, the cancer is incurable, with the average life expectancy being less than one year despite the best available treatments. It is recognised that the best chance of curing these tumours will be first of all to understand the nature or biology of the tumour, and then develop therapies targeted at the biology. These are called “biological therapies”.



Over the past ten years there has been a considerable increase in our understanding of cancer generally, and brain tumours specifically – at both a cellular and a molecular level. No longer are we limited in our knowledge to what the tumours look like generally, but molecular biology tools and techniques developed during the 1990s have given us an insight into the molecular structure of cancers, including the genetic aberrations and consequent abnormalities of gene expression.

We do believe that over the next ten years it will be possible for us to use our understanding of brain cancers to develop new therapies. Our laboratories have made considerable progress in developing potential “novel” targets for biological therapies, and we have every expectation that it will be possible to develop effective therapies for brain cancer in the future. However, further funding is vital to enable the work to continue.

Our laboratories are in a very special position, in that we are able to



collaborate closely with many national and international research institutes thereby increasing the rate of the progress of science.

Brain Tumour Research Program

The Brain Tumour Research Program is undertaken in the laboratories of the Department of Surgery at the University of Melbourne, and has close interaction with the Ludwig Institute for Cancer Research, the Walter and Eliza Hall Institute for Medical Research and other university departments.

The laboratory research primarily investigates the basic molecular and cellular events that lead to the development of brain cancer. This includes studying the role of cell-surface receptors in brain cancer growth and invasion and the intracellular signalling pathways that are altered in cancer development. Particular interest has been in defining the negative regulators of growth signalling pathways and compounds have been identified which can interact and either positively or negatively regulate the aberrant pathways.

Dr Peter Lock from the Department of Surgery is studying the role of the Tks5-Nck signalling pathway in brain tumour invasion.

Doctor Chris Hovens, in conjunction with his co-workers in a Phase 1 trial have established a compound which inhibits the PI3-AKT pathway, thought to be particularly important in brain tumours and prostate cancer. A patent has been awarded for this compound, and venture capital raised to commence a clinical trial at The Royal Melbourne Hospital.

Brain Tumour Program - Studies to isolate and characterize the biology of glioma stem cells (Cancer)

There is strong evidence that glioma tumours originate from small populations of malignant “brain tumour stem cells”. Unlike the bulk of the cells within a tumour, brain tumour stem cells have an unlimited potential to multiply and moreover, these cells are highly resistant to chemotherapy and radiotherapy. These cells are therefore thought to represent the primary source of brain tumours and are widely thought to be the most relevant cell type to target when conceiving future therapeutic approaches. On this basis we have begun to isolate brain tumour stem cells from specimens taken from patients receiving treatment at the Royal Melbourne Hospital and are in the process of establishing permanent stocks of the cells for research purposes. The brain tumour stem cells will be implanted into the brains of laboratory mice in order to develop animal models that will closely recapitulate the biology of the original brain tumours. This research will provide a clearer understanding of

the brain tumour biology and should enable the development of better, more targeted treatments of this devastating group of diseases.

Brain Tumour Program - Studies relating to epithelial-mesenchymal-endothelial-transition (EMET) and the role of TGF-beta in EGF receptor-driven tumorigenesis, with the aim of gaining a better understanding of tumour vascularisation (Cancer)

The majority of tumour death occurs due to tumour metastasis. Both tumour growth and tumour spread require angiogenesis, which is thought to be driven by the tumour but originated from host endothelial cells. Could tumour cells behave and function like endothelial cells? This application aims to detect the transition of adult epithelial cells to endothelial cells through a transient mesenchymal state. Our studies should reveal both the molecular and cellular causes of vasculogenic mimicry thus establishing a new paradigm in understanding tumour growth and metastasis. Such novel molecular understanding will open up new anti tumour therapeutic opportunities.

Brain Tumour Program – Molecular and Cellular Mechanisms of the Role of Epilepsy in Patients with Brain Tumours

In conjunction with the Department of Medicine, researchers from the Department of Neurosurgery are investigating the molecular mechanisms of epilepsy in patients with brain tumours. Dr Tanya Yuen was awarded the Sir John Lowenthal Research Fellowship from the Royal Australasian College of Surgeons to continue her work which is progressing towards a PhD on the molecular and cellular mechanisms of the development of epilepsy in patients with brain tumours. In particular, she is looking at the role of glutamate and its receptors and ADAM 22. This work may have considerable implications beyond epilepsy and brain tumours and help to understand the pathogenesis of epilepsy in those patients without a structural lesion. Dr Yuen's supervisors are Professor Andrew Kaye and Associate Professor Terry O'Brien.

Brain Tumour Program - Studies of the neurobiological mechanism involved in the development of epilepsy in brain tumour patients (Cancer)

Epileptic seizures commonly occur in patients with brain tumours, and are often difficult to control with anti-epilepsy medication. This causes significant morbidity and decreased quality of life for affected patients. The underlying cause(s) of such seizures remains unknown. Moreover this remains a poorly investigated field of research. We hypothesise that there will be identifiable factors involved in the development of these seizures, providing novel insight into their pathogenesis. This process will thus

identify novel targets for the development of new medications in the treatment of this disease. This will ultimately better equip clinical practitioners for the care of these patients.

Brain Tumour Program – Photodynamic Therapy

The department continues to study the use of photodynamic therapy to treat brain tumours and the laboratory investigations augment the clinical research program, by identifying new photosensitisers compounds, and enhancing the mechanism of the phototherapy action at a cellular and molecular level.

The department participates in numerous brain tumour clinical research programs at both a national and international level. This includes participation in the NH & MRC special government initiative on the relationship between

mobile telephone usage, electromagnetic radiation and the development of brain tumours. Numerous studies involved in the use of chemotherapy agents and the treatment of brain tumours have been investigated as part of Phase I, Phase II and Phase III Multicentre Trials. Members of the department have been instrumental in developing management guidelines for the treatment of brain tumours.

Intracranial Aneurysms

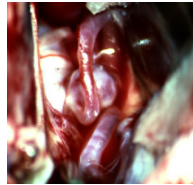
An aneurysm is an abnormal dilatation of a blood vessel, usually an artery, due to a weakness in its wall. Intracranial aneurysms are most commonly saccular, and have the appearance of a discrete bulge on the side of an artery. Because of their shape they are also often called "Berry" aneurysms. These arteries carry high-pressure blood to the brain, and the aneurysms usually occur where the arteries are branching under the brain.



Intracranial aneurysms are very rare in childhood, and usually occur in adults, presenting with increasing frequency with advancing age. They occur slightly more commonly in females than males. Although some families have a high

incidence of aneurysms, most occur sporadically and it is not generally considered to be an inherited condition. Most people who develop aneurysms are otherwise fit and healthy, although some rare connective tissue, kidney and blood vessel diseases are associated with an increased risk of developing aneurysms. Smoking and high blood pressure are also thought to increase the risk of aneurysm formation.

Aneurysms usually cause no symptoms at all until they rupture. Although the diagnosis of an aneurysm is occasionally made coincidentally in people who have scans for other reasons (eg after head injury, etc), most people with aneurysms are totally unaware of their presence, often for many years. There is currently some controversy regarding the risk of such an asymptomatic aneurysm rupturing, although we generally believe that it is probably less than 1% per year in most cases. Therefore, people with coincidental aneurysms are strongly advised that they do have time to seek specialist advice from a neurosurgeon who specialised in aneurysm treatment (cerebrovascular neurosurgeon), and to consider the treatment options.



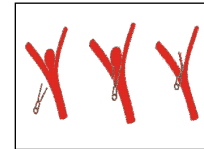
However, most aneurysms only become apparent when they do actually rupture, and this is a neurosurgical emergency. Aneurysm rupture causes sudden high-pressure bleeding into the fluid (CSF) which surrounds the brain and spinal cord. This is called subarachnoid haemorrhage (SAH). SAH typically causes an abrupt onset of headache, often with vomiting and neck stiffness, and not infrequently can cause sudden loss of consciousness and even sudden death. Occasionally the aneurysm can burst directly into the brain (intracerebral haemorrhage), causing paralysis or loss of speech or other symptoms commonly attributed to stroke.

People with these symptoms are rushed to hospital and the diagnosis of subarachnoid haemorrhage or intracerebral haemorrhage is typically made when an emergency CT scan shows the blood around or in the brain. Occasionally a sample of CSF is also tested to detect the blood. Although the CT scan is excellent at demonstrating the bleeding, it usually does not show the aneurysm itself, and the patient usually needs a specialised blood vessel xray (angiogram) to demonstrate the aneurysm.

At this time the aneurysm has temporarily sealed itself with a fragile clot over the rupture site, and the main concern is that the aneurysm will bleed again. This rebleeding is a devastating complication, with between 40-60% of rebleeding patients in hospital

dying. The risk of rebleeding is highest in the first 12-24 hours after the initial SAH, with about 10-17% of SAH patients rebleeding during this time.

Although rest, blood pressure control and pain relief have traditionally been used to reduce the risk of rebleeding, the only effective way to prevent rebleeding is to mechanically secure the aneurysm. This can be done with microsurgery, using the operating microscope to expose the vessels under the brain and applying a clip around the neck of the aneurysm to seal it off from the circulation.



Alternatively the aneurysm can be secured by endovascular treatment (that is by passing fine tubes through the blood vessels under xray control into the aneurysm, and then introducing fine platinum coils (or occasionally other devices or substances) into the aneurysm and blocking it off internally). Both treatments are highly specialised and delicate procedures. The choice between microsurgery or endovascular treatment depends primarily on the architecture of the blood vessels and aneurysm, and is ideally made by a cerebrovascular neurosurgeon in consultation with an interventional radiologist.

After the aneurysm has been secured, the patient is still at risk of developing other complications over the next 1-3 weeks. The blood around the brain can irritate the blood vessels causing spasm of arteries, which if untreated can cause stroke. The blood also disrupts the normal flow of CSF around the brain, causing build up of this fluid (hydrocephalus) which can require drainage or shunting. Patients also need to be closely watched for fluid and electrolyte abnormalities, heart rhythm problems, chest infection and blood clots in the legs. Therefore most patients are monitored in a specialised neurosurgical high-dependency unit.

Many patients who survive the initial SAH, particularly those who arrive at hospital with a good conscious state, do make a complete recovery, often being discharged to home within 1-2 weeks. However, some patients have brain injury from either from the initial aneurysm rupture, rebleeding, treatment of the aneurysm, or because of vasospasm. Depending on the extent of the brain injury, these patients' disabilities may range from relatively minor and transient, to profound and permanent (even causing death in some cases). Patients with disabilities usually benefit from rehabilitation after the acute hospital stay.

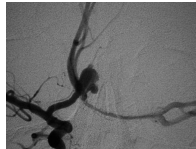
Intracranial Aneurysm Research

International Familial Aneurysm Study

This project, lead by Mr John Laidlaw studies those patients that could be at risk from development of cerebral aneurysms due to a genetic basis. In the past it has been considered that there was no direct inheritance of the risk to develop cerebral aneurysms, but more recent investigations have shown the possibility of an inherited basis. This is a large international investigation, which will help study the genetic basis for the development of cerebral aneurysm, through identification of those families with familial aneurysms.

CT Angiography in the Diagnosis and Treatment of Cerebral Aneurysms (Dr John Laidlaw)

Mr Laidlaw is also studying the role of CT angiography, and its possible replacement for conventional angiography in the diagnosis and management of patients with intracranial aneurysms. This would potentially significantly reduce the morbidity associated with cerebral angiography in these very sick patients.



Neuro-Endocrinology and Pituitary Tumours

A number of clinical studies are being undertaken into the management of patients with pituitary tumours in conjunction with members of the Department of Endocrinology. Mr Nicholas Maartens has developed a comprehensive database to identify those clinical and laboratory factors that will optimise the management of patients with pituitary tumours. International collaborations are numerous and include countries as diverse as the United States of America (Stanford University) and Iran (Tehran University). Members of the Department participated in a study with the Department of Endocrinology which has resulted in redefining the use of steroid medication following pituitary surgery. This has now been adopted internationally.

Neuro-Endocrinology and Neuro-Ophthalmology

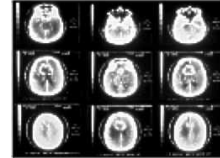
The Use of Optical Coherence Tomography and the Prediction of Visual Outcome in Optic Compressive Pathology (Professor Andrew Kaye, Dr Niki Maartens, Dr Mark Daniell).

In conjunction with investigators from Auckland University the Department is undertaking a study of the use of optical coherence tomography to measure the retinal nerve fibre layer and predict visual outcome following surgery for optic compressive pathology. This has considerable implications in terms of managing patients with brain tumours and other pathology that compresses the optic nerve and

chiasm. Preliminary data has been presented at the International Pituitary Society Meeting in Vienna.

Brain Trauma

The department is involved in a number of clinical research studies involving the optimal management of patients with serious brain injury. This includes a national collaborative study of the use of decompressive craniectomy for patients with severe head injury.



Awards and Grants

- NHMRC - Dr Hong Jian Zhu - The Role of TGF- β Signaling in Suppression of Stat3 mediated Tumorigenesis.
- NHMRC - Dr Hong Jian Zhu - How does abnormal regulation of Src-family kinase cause cancer
- NHMRC - Dr Hong Jian Zhu - Differential Cooperation of MAPKs with TGF- β Signaling in Epithelial-Mesenchymal Transition
- CCV - Dr Hong Jian Zhu - Regulation of PTEN Activity and Subcellular localisation.
- NHMRC - Dr Hong Jian Zhu - How does abnormal regulation of Src-family kinase cause cancer
- NHMRC - Dr Christopher Hovens, Professor Andrew Kaye - A developmental drug for the treatment of brain tumours.
- Velacor Therapeutics Pty Ltd - Dr Christopher Hovens, Professor Andrew Kaye - Preclinical evaluation of VELO15 compound for cancer treatment
- Brain Foundation - Dr Peter Lock, Professor Andrew Kaye - The role of Tks5 in malignant glioma invasion
- Cure for Life Foundation - Dr Peter Lock, Professor Andrew Kaye & Stan Stylli - The role of Tks5 in malignant glioma invasion
- Neurosurgical Research Foundation of Australasia - Dr Peter Lock, Professor Andrew Kaye - Evaluation of the role of ARAP3 as a suppressor of malignant glioma invasion
- RMH Neuroscience Foundation - Professor Andrew Kaye - Brain Tumour Research Program

Current Funding Sources

- Medtronic
- Johnson & Johnson Depuy Spine
- Johnson & Johnson Codman
- Lifehealthcare

- John T. Reid Charitable Trusts
- Melbourne Private Hospital
- NHMRC, Dr Hong-Jian Zhu
- NHMRC, Dr Christopher Hovens, Professor Andrew Kaye
- Cancer Council of Victoria, Dr Hong Jian Zhu
- Brain Research Foundation, Dr Peter Lock, Professor Andrew Kaye
- Cure for Life Foundation, Professor Andrew Kaye
- Cure for Life Foundation, Dr Peter Lock, Professor Andrew Kaye
- Cure for Life Foundation, Rodney Luwor
- MDHS, The University of Melbourne
- The Royal Melbourne Hospital Neuroscience Foundation, Professor Andrew Kaye
- Neurosurgery Research Foundation, Dr Peter Lock, Professor Andrew Kaye
- The University of Melbourne, Rodney Luwor
- Urology Trust, Dr Chris Hovens
- Velacor Therapeutics Pty Ltd, Dr Christopher Hovens, Professor Andrew Kaye
- Western and Central Melbourne Integrated Cancer Service, Dr Kate Drummond

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