The Genetics of Brain Tumours

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Cancer: Brain Tumour, 
first thoughts 
(2007)

Painting by Mary Stebbins Taitt 
shortly after she was diagnosed 
with a brain tumour
Why are brain tumours so difficult to treat?
1. BRAIN TUMOURS ARE HIGHLY INVASIVE
2. BRAIN TUMOURS ARE HIGHLY RESISTANT TO THERAPY

Chemotherapy agents such as Temodal kill tumour cells by breaking their DNA.

Tumour cells have high levels of proteins that repair the DNA breaks caused by the chemotherapy. Thus: No effect.
3. BRAIN TUMOURS ARE GENETICALLY DIVERSE

• All three samples are diagnosed as a high grade tumour by pathology
Everyone’s tumour is genetically different

Heat map courtesy of Dr T Cloughesy, UCLA
gene expression

exon expression

micro RNA expression

protein expression

Loss of miRNA

Alternative splicing

mRNA

ribosome

ribosome

protein

aberrant protein
Team Brain

Cathy Payne
PhD
Currently at Duke Uni, USA

Hatice Sevim
Masters/ PhD

Sanaz Maleki
Research Assistant

Dr Adam Fowler
PhD

Plus
Pituitary Research
Ann McCormack (PhD)
Marianne Elston (PhD)

Newcomers
Sophia Roser (Med Hons)
Bryan Tan (Sci Hons)
Research Assistant

Clinical Database
Sally Fielding

Clinical Associates: Prof Bruce Robinson, Dr Helen Wheeler, Dr Ray Cook, Dr Michael Biggs, Dr Nick Little
The research begins with tumour banking

- Australian Brain Tumour Bank (ABTB)
- Established in 2003 by Professor Bruce Robinson (USyd) and Dr Ray Cook (RNSH, SNOG)
- Fully operational in 2005
  - Never miss capturing a tumour of brain origin
- Over 800 brain tumour specimens
  - GBM
  - Different grades of glioma
  - Meningiomas
  - Pituitary tumours
  - Metastases
  - Spinal
  - Neural
The tumours new home!

Tumour Bank is a -80°C Freezer located in Cancer Genetics at the Kolling Institute of Medical Research.

Tumours are decoded and given a nominated position in the bank.

All staff are given specialised training in handling the precious tumour.
Collaborations formed as a result of the Australasian Brain Tumour Bank

- **Examining the incidence of ALT in GBM**
  Prof. Roger Reddel (CMRI), Dr Janice Royds (University of Otago, NZ) & Monika Hegi (Lausanne, Switzerland)

- **Investigating the methylation patterns of genes lying within the 1p and 19q chromosomal arms in oligodendroglialomas**
  Dr Michael Buckland (St Vincents/ Victor Chang)

- **Arc1 and survivin: Anti-apoptotic proteins and predictors of poor survival**
  Dr David Ziegler (Sydney Children’s Hospital)

- **Understanding the mechanisms of long term survival in GBMs**
  Dr Charlie Teo (POW)

- **Australian Genomics and Clinical Outcomes of Glioma**
  Prof Lyle Palmer (WAIMR)

- **microRNA and Glioma**
  Prof Peter Leedman (WAIMR)
Can we find genes that cause aggressive high grade brain tumours?
Identifying discriminating genes

High Grade Brain Tumours  Low Grade Brain Tumours

KPNA5  Homer1  YKL-40  LGALS1  IGFBP2  IQGAP1  RBP1  COPZ2  SPP1  SERPINA3  ARS  LRRRC20  HS75LP  C1QL1  CARHSP1  HSxS138  NFYB  KIAA0599
Low grade brain tumours: n=75
High grade brain tumours: n=62

McDonald et al. 2007 JNEN 66, 405-417
IQGAP1: A key protein involved in migration

- Stem cells that go onto form brain tumours express high levels of IQGAP1
- High expression patterns of IQGAP1 are typically associated with poor survival
- It is a useful marker to determine prognosis in the anaplastic grade of tumour (grade III)
- Long term GBM survivors (3 years+) typically do not express IQGAP1

Because of all these reasons, the lab is focusing on IQGAP1—what causes it to be overexpressed, does it regulate migration, how can we turn it off?
IQGAP1 overexpression in vitro

Knock-down expression with an IQGAP1-specific siRNA

Dr Adam Fowler
1st year PhD
Loss of IQGAP1 impedes cell migration
TEMODAL CILENGITIDE

NOVEL AGENTS
MICRO RNA THERAPY
Can we find molecular markers that could tell us which low grade tumour is likely to progress?
Prostaglandin D2 synthase expression is lost as an astrocytoma becomes more malignant
PGDS has tumour suppressor properties

- We over-expressed PGDS in GBM cell lines
  - This led to reduced cell proliferation
  - The cells were more responsive to COX-2 inhibitor therapy

- The downstream product of PGDS, PDG$_2$ when added back to the cell lines, also exhibited tumour suppressor properties

Payne et al., 2008 Mol Cancer Ther 7(10) October
3. BRAIN TUMOURS ARE GENETICALLY DIVERSE

- TUMOUR RECURRENCE SOON AFTER SURGERY (POOR RESPONSE)
- GOOD RESPONSE TO THERAPY BUT TUMOUR RECURS
- NO TUMOUR RECURRENCE AFTER SURGERY OR THERAPY

POOR SURVIVAL FAVOURABLE
“One drug fits all” treatment approach

Patients with high genetic variability

Surgical Debulking → Pathology

HGG

Radiotherapy → Concurrent Chemotherapy

Concurrent Chemotherapy

TMZ

3 out of 4 patients fail this treatment

Adjuvant Chemotherapy

Test for known biomarkers

Mutation

Microarray

Storage of frozen tissue in a Tumour Bank

Salvage Therapy

Typically too late

Tumour Recurrence
The Ideal Predictive Marker

The assay needs to be reliable

- The assay needs to give the same results if repeated in the same or in another laboratory.

- The result needs to be the same, even when different methodologies are used.

- What added value does this test have?
Work is underway to develop new and robust biomarkers to help guide neuro-oncologists in their treatment decisions.

- EGFRvIII
- PTEN
- Topollalpha
- MGMT
- MSH2 and 6
- New proteins identified from arrays

AUTOSTAINER THAT CAN PROCESS OVER 140 SLIDES PER DAY

STATE OF THE ART FLUORESCENCE MICROSCOPE WITH DIGITAL CAMERA SYSTEM

CALEDONIA FOUNDATION 2007
The Future of Treatment for Brain Tumour

1. TUMOUR BANKING

2. AFFYMETRIX CHIP TECHNOLOGY

3. PROFILING OF GENES

4. TEST DESIGN

5. IMPLEMENT THE TEST

- temozolomide
- Alkylating agents
  - thalidomide
  - etoposide
- erlotinib
- Non-telomerase targeted treatment

CALEDONIA FOUNDATION 2007
TCGA: The Cancer Genome Atlas Research Network

- Collaborative effort funded by the National Cancer Institute (NCI) and the National Human Genome Research Institute (NHGRI) of the National Institutes of Health (NIH)

- The NCI and NHGRI initiated TCGA in 2006 to accelerate understanding of the molecular basis of cancer through the application of current genome characterisation technologies including large-scale genomic sequencing
A Public Resource

- All TCGA data is deposited at the Data Coordinating Centre (DCC) for public access
  
  http://cancergenome.nih.gov
Australian Genomics and Clinical Outcomes of Glioma (AGOG)

- AGOG is a new national brain tumour network funded by a 5 year Strategic Research Partnership Grant from the Cancer Council NSW

- Comprises an experienced, multi-disciplinary team of clinicians and scientists
AGOGs Major Objective

- To establish a research resource with focus on:
  - Clinical Care Patterns
  - Functional Genomics
  - Genetic Epidemiology
We propose to examine current treatment and referral patterns and to identify genes and proteins associated with diagnosis, disease progression and treatment response via the collection of:

- Clinical data
- A blood sample for DNA, RNA, plasma and serum collection
- Fresh tumour tissue sample for identifying biological markers
Minimal Achievements

- National Tumour Banking
  - All patients around Australia and NZ will be given the opportunity to have their tumour frozen. This grant provides infrastructure to do so.

- National Epidemiological Study
  - We still don’t fully understand the risk factors

- Working together, as one!!
Here’s to the future!!!

Thank you

Cure For Life Foundation
Caledonia Foundation

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Sydney Neuro-oncology Group
Andrew Olle Foundation
Cancer Council NSW
Cancer Institute NSW
CSIRO

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Cathy Payne
Dr Helen Wheeler
Dr Charlie Teo
Dr Raymond Cook
Prof Bruce Robinson