Institution: Newcastle University

Unit of Assessment: UoA1

Title of case study: Treatment stratification for childhood medulloblastoma patients

Period when the underpinning research was undertaken: 2005-2017

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Prof Steve Clifford	Professor of Molecular Paediatric Oncology	1/10/00 to present
Prof Simon Bailey	Honorary Clinical Professor	1/2/00 to present
Prof David Ellison	Professor of Neuropathology	1/1/01 to 12/10/06
Dr Ed Schwalbe	PhD Student	1/12/10 to 30/10/13
Dr Janet C Lindsey	Research Associate	5/6/00 to 13/10/19
Dr Meryl E. Lusher	School Manager	1/11/02 to 18/10/20
Dr Sara L Ryan	PhD Student	1/10/09 to present
Dr Debbie Hicks	University Research Fellow	14/12/04 to present
Mr Kieran O'Toole	Research Officer	1/10/02 to 30/4/10
Dr Daniel Williamson	Lecturer	1/6/10 to present
Dr Reza Rafiee	Research Associate	20/1/14 to 31/5/17
Dr Matthew Bashton	Research Associate	10/10/11 to present
Dr Amir Enshaei	Senior Research Associate	3/10/11 to present
Dr Steve Crosier	Advanced Biomedical Research Scientist	1/12/11 to present
Ms Amanda J Smith	Technician	16/4/12 to 31/3/18
Dr Michael Mather	MRes Student	5/2/20 to present
Miss Pim Taleongpong	Undergraduate Student	1/10/14 to 31/3/16
Mr Sandeep Potluri	NHS Academic Fellowship Programme	2013 to 2015
Miss Jessica Matthiesen	Undergraduate Student	2013 to 2014
Dr Dolores Hamilton	PhD Student	2009 to 2013
Dr Debbie Straughton	PhD Student	2002 to 2006
Dr Hisham Megahed	PhD Student	2006 to 2010

Period when the claimed impact occurred: 2013–present

Is this case study continued from a case study submitted in 2014? No

1. Summary of the impact

Medulloblastoma accounts for ~10% of all childhood cancer deaths. With aggressive treatment ~70% of children with medulloblastoma can expect to be free of disease 5 years later, but it was not clear how to identify them. Newcastle research identified and/or validated 4 distinct molecular subgroups (WNT, SHH, Group 3 and Group 4) which stratified patients into excellent prognosis or poor prognosis groups. These four sub-groups are now internationally recognised and are considered 'standard-of-care' for the disease, summarised in an international consensus paper, and underpin the 2016 WHO classification of medulloblastoma. Additionally, the WNT biomarker is guiding patient stratification and personalised treatment in 3 international clinical trials. Newcastle also hosts the national reference centre for medulloblastoma diagnostics, providing real-time advanced molecular diagnostics, including assays developed in Newcastle, for all patients in the UK.

2. Underpinning research

Unmet need

Medulloblastoma is the most common malignant brain tumour in children, accounting for 10-20% of primary central nervous system (CNS) neoplasms and approximately 40% of all posterior fossa tumours. Ultimately, medulloblastoma accounts for approximately 10% of all childhood cancer deaths. Medulloblastomas are highly invasive embryonal neuroepithelial tumours which arise in the cerebellum and have a tendency to disseminate throughout the central nervous system early in their course. With aggressive surgery, craniospinal radiotherapy and chemotherapy, around 70% of children with medulloblastoma can be expected to be free of disease 5 years later.

However, treatment often results in significant long-term adverse endocrinological, neurological and intellectual sequelae. These can involve the child not being able to go to school, or live independently, leading to the attendant long-term disadvantage. Before Newcastle research, identification of which 70% of children would be disease-free was not possible.

Stratification of medulloblastoma

There are approximately 55 new cases of childhood medulloblastoma in the UK every year[1] and tumours caused by mutations in the WNT signalling pathway account for approximately 11%[2]. β-catenin is the major effector for WNT signalling pathway function. Newcastle discovered that β-catenin protein presence in medulloblastoma tumours is a biomarker for a good prognosis (R1 and R2). Patients who were β-catenin positive had a 5-year overall survival of 92.3% and event free survival of 88.9%, compared with 65.3% and 59.5% respectively for β-catenin negative patients (R1). Newcastle research also found that WNT positive tumours, identified by the β-catenin biomarker, represented a distinct molecular subgroup of tumours characterised by mutations in the *CTNNB1* gene (which encodes β-catenin) and loss of an entire copy of chromosome 6, but few other genetic abnormalities (R3).

Further investigation of medulloblastoma cohorts also identified the SHH, Group 3 and Group 4 subgroups, each associated with distinct clinical characteristics (e.g. survival outcomes) and molecular disease features (R4, R5, R6). The WNT subgroup have the best survival rates while Group 3 has the worst prognosis. Group 4 and SHH both have an intermediate prognosis except in infants where SHH has a good prognosis (R5). Newcastle research also demonstrated that analysis of DNA methylation patterns could be used to detect these biomarkers and improve the subsequent disease-risk stratification (R6, R7).

These subgroups are now internationally recognised as new classifications for medulloblastoma. WNT, in particular, is now being used proactively to predict prognosis and stratify patients into appropriate trial arms in which patients receive suitable innovative treatment matched to their disease biology.

3. References to the research

SciVal field-weighted citation impact (FWCI) as of December 2020. Newcastle researchers in **bold.**

R1. **Ellison DW**, Onilude OE, **Lindsey JC**, **Lusher ME**, Weston CL, Taylor RE, Pearson ADJ, **Clifford SC**. (2005) β-catenin status predicts a favorable outcome in childhood medulloblastoma: the United Kingdom Children's Cancer Study Group Brain Tumour Committee. *Journal of Clinical Oncology*. 23(31):7951-7957. DOI: 10.1200/JCO.2005.01.5479. FWCI: 3.87.

R2. **Clifford SC**, Lannering B, **Schwalbe EC**, **Hicks D**, **O'Toole K**, **Nicholson SL**, Goschzik T, Zur Mühlen A, Figarella-Branger D, Doz F, Rutkowski S, Gustafsson G, Pietsch T; SIOP-Europe PNET Group. (2015) Biomarker-driven stratification of disease-risk in non-metastatic medulloblastoma: Results from the multi-center HIT-SIOP-PNET4 clinical trial. *Oncotarget*. 6(36):38827-39. DOI: 10.18632/oncotarget.5149. FWCI: 1.46.

R3. **Clifford SC**, **Lusher ME**, **Lindsey JC**, Langdon JA, Gilbertson RJ, **Straughton D**, **Ellison DW**. (2006) Wnt/Wingless pathway activation and chromosome 6 loss characterise a distinct molecular sub-group of medulloblastomas associated with a favourable prognosis. *Cell Cycle*. 5(22):2666-2670. DOI: 10.4161/cc.5.22.3446. FWCI: 0.07.

R4. **Ellison DW**, Kocak M, Dalton J, **Megahed H**, **Lusher ME**, **Ryan SL**, Zhao W, Nicholson SL, Taylor RE, **Bailey S**, **Clifford SC**. (2011) Definition of Disease-Risk Stratification Groups in Childhood Medulloblastoma Using Combined Clinical, Pathologic, and Molecular Variables. *Journal of Clinical Oncology*. 29(11):1400-1407. DOI: 10.1200/JCO.2010.30.2810. FWCI: 6.87.

R5. Kool M, Koster J, Bunt J, Hasselt NE, Lakeman A, van Sluis P, Troost D, Meeteren NS, Caron HN, Cloos J, Mrsić A, Ylstra B, Grajkowska W, Hartmann W, Pietsch T, Ellison D,

[1] https://www.cancerresearchuk.org/about-cancer/childrens-cancer/brain-tumours/types/medulloblastoma

[2] https://radiopaedia.org/articles/medulloblastoma-wnt-subgroup

Clifford SC, Versteeg R. (2008) Integrated genomics identifies five medulloblastoma subtypes with distinct genetic profiles, pathway signatures and clinicopathological features. *PLoS One*. 3(8):e3088. DOI: 10.1371/journal.pone.0003088. FWCI: 8.95.

R6. **Schwalbe EC**, **Williamson D**, **Lindsey JC**, **Hamilton D**, **Ryan SL**, **Megahed H**, Garami M, Hauser P, Dembowska-Baginska B, Perek D, Northcott PA, Taylor MD, Taylor RE, Ellison DW, **Bailey S**, **Clifford SC.** (2013) DNA methylation profiling of medulloblastoma allows robust subclassification and improved outcome prediction using formalin-fixed biopsies. *Acta Neuropathologica*. 125(3):359-71. DOI: 10.1007/s00401-012-1077-2. FWCI: 24.7.

R7. **Schwalbe EC**, **Hicks D**, **Rafiee G**, **Bashton M**, Gohlke H, **Enshaei A**, **Potluri S**, **Matthiesen J**, **Mather M**, **Taleongpong P**, Chaston R, Silmon A, Curtis A, **Lindsey JC**, **Crosier S**, **Smith AJ**, Goschzik T, Doz F, Rutkowski S, Lannering B, Pietsch T, **Bailey S**, **Williamson D**, **Clifford SC.** (2017) Minimal methylation classifier (MIMIC): A novel method for derivation and rapid diagnostic detection of disease-associated DNA methylation signatures. *Scientific Reports*. 7(1):13421. DOI: 10.1038/s41598-017-13644-1. FWCI: 4.4.

4. Details of the impact

The identification of WNT, SHH, Group 3 and Group 4 subgroups and their biomarkers has resulted in three main areas of impact; the international recognition of the 4 biomarkers as new classification of medulloblastoma; the use of the WNT biomarker to guide the treatments for 3 international trials; and the establishment of a national referral centre for medulloblastoma based in Newcastle, which uses these biomarkers in routine diagnosis.

<u>Impact on medulloblastoma classification</u>

Newcastle research (R1, R3, R4, R5) informed international consensus on the subgrouping of medulloblastoma, resulting in the 2012 paper "Molecular subgroups of medulloblastoma: the current consensus" (EV1). This consensus in turn informed "The 2016 WHO classification of tumors of the central nervous system" (EV2), a revised and updated version of the 2007 classifications. The 2016 WHO classifications state that:

> "*… it is now widely accepted that there are four genetic (molecular) groups of medulloblastoma: WNT-activated, SHH-activated, and the numerically designated "group 3" and "group 4" [EV1]. Some of these histological and genetic variants are associated with dramatic prognostic and therapeutic differences.*"

As a key, internationally recognised document, the 2016 WHO tumour classification defines and leads changes in diagnostic practice. In reference to combining histological and genetic information to reach an accurate diagnosis, the document itself states that:

> "*This modular and integrated approach to diagnosis is novel, but likely represents a method that will become more common as knowledge of tumor genetics and phenotype–genotype correlation grows.*" (EV2)

<u>Impact on patients and clinical trials</u>

Three major international clinical trials currently underway are using the WNT biomarker, as identified by Newcastle, to guide the radiotherapy treatment strategy of patients. In paediatric oncology, most children are treated within clinical trials and these therefore represent the current standard of care. Collectively the three trials are treating 124 WNT patients, under these risk-stratified treatment regimens, in Europe, North America and Australasia.

- SIOP-PNET5-MB (ClinicalTrials.gov ID: NCT02066220); a Cancer Research UK pan-European trial which began in 2013 and will run until 2021. Since 2015, 60 WNT patients have received altered craniospinal irradiation (CSI) treatment with doses reduced from 23.4Gray (Gy) to 18Gy and the frequency of post irradiation chemotherapy cycles reduced from 8 cycles to 6 (EV3).
- SJMB12 (NCT01878617); a clinical trial across North-America, Australia and New Zealand led by St Jude Children's Research Hospital, ending in 2022. Since 2013, 45 WNT patients have had their radiotherapy dose reduced from 24Gy to 15Gy and chemotherapy cycles reduced from 9 to 4 cycles (EV4).

- ACNS1422 (ClinicalTrials.gov ID: NCT02724579); a clinical trial of 200 centres in the US, Canada, Switzerland, the Netherlands, Australia and New Zealand co-ordinated by the Children's Oncology Group and National Cancer Institute (NCI). Since 2017, 19 WNT recruited participants have had their radiotherapy doses reduced from 23.4Gy to 18Gy with no vincristine during radiotherapy and chemotherapy reduced from 9 to 7 cycles (EV5).

As radiotherapy in medulloblastoma treatment targets the brain and central nervous system, reducing the radiation that a patient receives will reduce the damage done to the surrounding tissue. Patients taking part in these trials are therefore expected to have fewer cognitive impairments due to lower radiation levels during treatment (EV3, EV4, EV5). As of December 31st 2020, all 3 trials are continuing as planned, indicating that patients are responding as expected.

Establishment of the National Medulloblastoma Molecular Diagnostics Reference Centre

Newcastle research and the expertise located here, led to Newcastle establishing and hosting the National Medulloblastoma Molecular Diagnostics Reference Centre (EV6). Established in 2018 within the Newcastle upon Tyne Hospitals NHS Foundation Trust, this centre offers contemporary molecular testing of the identified biomarkers, underpinning national diagnostics for all children with medulloblastoma and screening for entry into SIOP-Europe Brain Tumour Group coordinated trials. The centre provides a centralised service of tests not typically available at local treatment centres and consequently coordinates the processing, analysis and reporting of samples from more than 20 local and regional treatment centres (EV6).

The Centre's feasibility was confirmed in early 2018 following recruitment and testing of 178 medulloblastoma patients. A further 109 patients have been assessed using the biomarker framework since routine clinical testing began in April 2018. This represents approximately 70% of children with medulloblastoma in the UK

The Centre's Clinical Director confirms that "*medulloblastoma patients now receive improved personalised care as a direct result of these discoveries ... the most intensive therapies are targeted to patients with high-risk disease, while clinical trials of reduced therapies are underway for patients with favorable risk disease (i.e. WNT subgroup patients; discovered by the Newcastle University Team).*" (EV6). This approach focuses on de-escalation strategies for low-risk patients; preserves average risk patients from risky de-escalation or unnecessary augmentation in therapy; and effectively targets poor responders for novel therapy.

Summary

Identification and validation of 4 medulloblastoma subgroups by Newcastle has informed WHO tumour classification; currently guides clinical practice of 3 international clinical trials by informing reduced irradiation dosing and chemotherapy cycles for 124 WNT patients; and underpins diagnostic testing of approximately 70% of the UK's childhood medulloblastoma patients.

5. Sources to corroborate the impact

EV1. Taylor MD, et al. (2012) Molecular subgroups of medulloblastoma: the current consensus. *Acta Neuropathologica*. 123:465-472. DOI: 10.1007/s00401-011-0922-z. PDF https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3306779/pdf/401_2011_Article_922.pdf

EV2. Louis DN, et al (2016) The 2016 WHO classification of tumors of the CNS – a summary. *Acta Neuropathologica*. 131(6):803-820. DOI: 10.1007/s00401-016-1545-1. PDF http://braintumor.org/wp-content/assets/WHO-Central-Nervous-System-Tumor-Classification.pdf

EV3. Letter of support from PNET 5 clinical trial leads. PDF available on request

EV4. Letter of support from SJMB12 clinical trial leads. PDF available on request

EV5. Letter of support from ACNS1422 clinical trial leads PDF available on request

EV6. Letter of support from the Clinical Director of the National Medulloblastoma Molecular Diagnostic Reference Centre, confirming the role of Newcastle in the establishment of the Centre. PDF available on request