CCLG/TOM GRAHAME TRUST GRANT

TITLE:
Biomarker and target discovery for the improved therapy of high-risk medulloblastoma.

FUNDING PERIOD:
1st September 2013 for three years.

GRANTHOLDERS:
Principal Investigator:
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And on behalf of the UK PNET group (ex- CCLG CNS Tumours Division).

PROJECT AIMS AND OBJECTIVES:
Aim: To discover biomarkers which can direct individualised therapy for high-risk medulloblastoma.
Hypothesis: Biomarkers required for the improved management of high-risk medulloblastoma are unique and distinct from standard-risk medulloblastoma.
Objectives: To undertake the largest and most comprehensive biological investigations of high-risk medulloblastoma patients (infants (*n>160*) and older children (n>200)) to date, using cohorts based on recent clinical trials.

PROGRESS IN YEAR ONE:
The project is progressing well and according to plan, as follows:

Cohorts: The project has focussed on instigating investigations in infant medulloblastoma (i.e. <5 years at diagnosis) in the first year. We have completed (i) sample collection and preparation for analysis, (ii) collection and review of clinical data and (iii) pathology review of our infant cohort, totalling 180 frozen and/or FFPE tumour biopsies. We will progress in year 2 to undertake equivalent preparation of our non-infant high-risk patient cohort, with ~200 such samples currently collected in Newcastle for assessment.

Data collection: DNA has been extracted from all infant medulloblastoma biopsies. The analysis of DNA methylation patterns in these samples by Illumina 450K methylation (450,000 CpG residues) has now been completed and was successful for 145 samples. We have developed methods to assess medulloblastoma subgroup status using these data [1] and applied these to determine subgroup status (WNT, SHH, Group 3 or Group 4) in our cohort. Further, we have developed methods for the generation and assessment of genomic copy number data using the Illumina 450K data. In addition, the status of established medulloblastoma biomarkers (e.g. MYC and MYCN amplification, TP53 pathway and mutation, and chromosome 17 status) has been assessed using specific assays.

Data analysis: This project has developed the largest collected series of biologically characterised infant medulloblastomas to date for analysis. We have now progressed to the data analysis stage of the infant project, which is currently underway. Our experienced team of bioinformaticians and statisticians are using conventional and innovative approaches to integrate the biological and clinical datasets we have generated to provide a detailed description of the clinical, pathological and biological features of the infant disease. Specifically, these are focussing on the identification of critical biological features which could be used to improve our ability to stratify treatment and predict risk. We anticipate completion and initial reporting of this first wave of data analysis over the coming year.

ANTICIPATED CLINICAL IMPACT:

Biomarkers discovered will support the development of new treatment strategies, including molecular disease-risk stratification and delivery of targeted therapeutics. Findings will be incorporated into planning future medulloblastoma trials, through our leading roles in National and European trials, and our ongoing biological research programme, together aimed at delivering improved outcomes.

REFERENCES:

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 Neuropathol. 125: 359-71.