Research proposal for the Andrew McCartney Trust Fund – June 2019

Examining the metabolism of Childhood Brain Tumours using Mass Spectrometry.

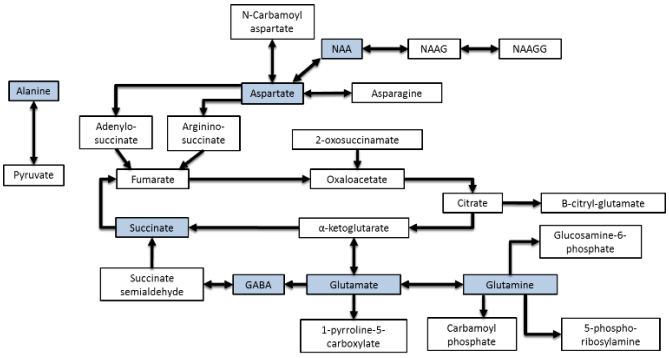
Research summary

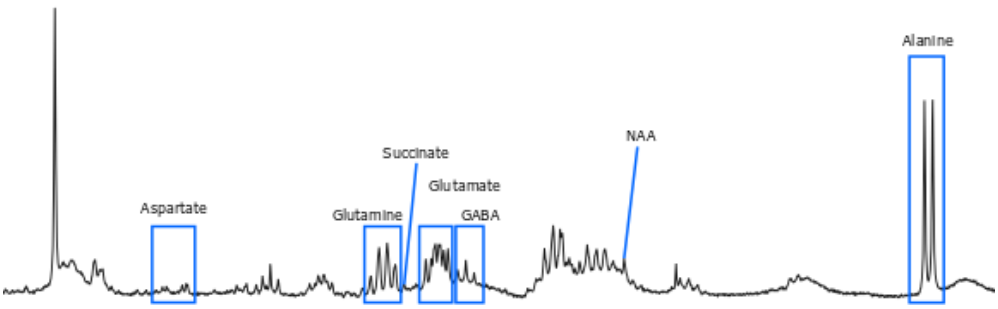
An aspect of our research investigates the chemicals (metabolites) that are found in brain tumours. The amount of certain metabolites in a tumour can tell us what type of tumour the tissue came from, as well as how aggressive the tumour is likely to be. We have recently begun to investigate how groups of biologically related metabolites in metabolite pathways are most altered between tumour types. Further work is required to understand how different tumours alter their metabolism.

Background

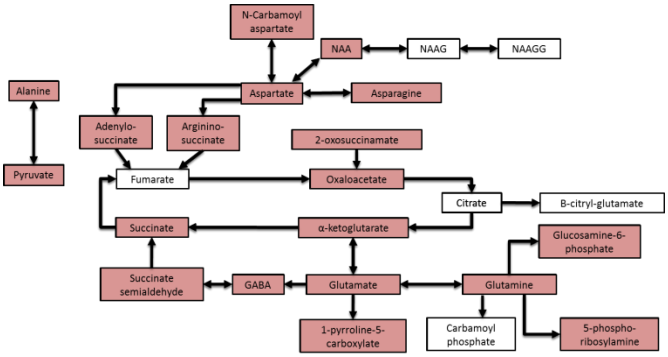
Using Magnetic Resonance Spectroscopy (MRS) of surgically removed tumour tissue we can measure the concentration of around 30 metabolites. Metabolites are organised into metabolic pathway based on their possible biological reactions. By performing a metabolic pathway analysis we can see which metabolic pathways are altered between tumours. Pathways we have identified as being different between brain tumours include the alanine, aspartate and glutamate pathway, serine, glycine and threonine pathway and taurine hypotaurine pathway.

MRS is suffers from relatively low sensitivity, and can only detect a small number of metabolites within a pathway. As shown below, of the 24 metabolites within the alanine, aspartate and glutamate metabolic pathway, MRS can detect 7 metabolites (highlighted in blue). The corresponding features are shown in an example spectrum. So whilst MRS can detect pathways that are different between tumours, it is difficult to identify important differences within the pathways of interest.





Mass spectrometry is another technique that can measure the amount of metabolites in a tumour. It is far more sensitive than MRS, and is able to measure many more metabolites. As an illustration, mass spectrometry can detect 19 of the 24 metabolites of the alanine, aspartate and glutamate pathway as shown below with detectable metabolites highlighted in red along with an example mass spectrum. This gives us the potential to study tumour metabolism in much greater detail.



We have acquired data from an existing cohort of tissue, and have performed pathway analysis. The next step is to further mine the data, and reconstruct metabolic networks from the mass spectrometry data. Networks such as these will allow us to examine the metabolism of these tumours beyond pathway analysis and identify which metabolite interactions are most important for particular brain tumours.

Proposal aim – to further our understanding of brain tumour metabolism using mass spectrometry and data mining statistical techniques. This will enable us to increase our understanding of how different tumours alter their metabolism, especially with regards to the lipid metabolites.

Brief Plan and Objectives

1. Mass spectrometry data has already been collected from a range of tumour types through facilities in place at the University of Birmingham. So far, open source software has been used to perform the analysis. However, commercially available software would provide more robust analysis options. Therefore, we will identify potential software to aid in processing and analysing the data.
2. Various statistical techniques, including network analysis will be performed on the mass spectrometry data for each tumour type to reconstruct the metabolic network. This will allow us to identify differences in the metabolism of tumours.
3. Further mass spectrometry will be performed on more samples to balance the various tumour groups in the original analysis.

Expected Outcomes

Our current mass spectrometry data has demonstrated a substantially increased number of detected metabolites relative to MRS. This increased richness of data will allow us to start unravelling how

different tumours use their chemical resources. Identification of important metabolic reactions within tumour groups may lead to identification of novel therapeutic targets.

Proposed project start date of 1 July 2020: