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| **The Institute of Cancer Research** PHD STUDENTSHIP PROJECT PROPOSAL: | | |
| **PROJECT DETAILS** | | |
| **Project Title:** | Single cell approaches to understanding gliomatosis cerebri | |
| **Short Project Title:** |  | |
| (If main project title is >120 characters including spaces) | Single cell approaches to understanding gliomatosis cerebri | |
| **SUPERVISORY TEAM** | | |
| **Primary Supervisor(s):** | | Chris Jones |
| **Associate Supervisor(s):** | | TBA |
| **Backup Supervisor:**  (must have IRS status) | | Janet Shipley |
| **IRS Partner :**  (only required where Primary is a CDF, Associate Honorary Faculty or an ICR Fellow – ***see above***) | |  |
| **Lead contact person for the project:** | | Chris Jones |
| **DIVISIONAL AFFILIATION** | | |
| **Primary Division:** | | Molecular Pathology |
| **Primary Team:** | | Glioma |
| **Other Division (if applicable):** | |  |
| **Other Team (if applicable)):** | |  |
| **PROJECT PROPOSAL** | | |
| **BACKGROUND TO THE PROJECT (up to 300 words)** | | |
| Gliomatosis cerebri (GC) is a rare brain tumour that mostly affects children and young adults. Unlike other brain tumours, little is known about this type of cancer, and survival is very poor, with most patients succumbing to their disease within 18 months of diagnosis. GC is a radiological diagnosis rather than a pathological one, as there appear to be few histological or molecular differences between GC biopsy samples and those from established diffuse glioma subgroups. We hypothesise that the unique infiltrative phenotype of GC may be driven by extensive intratumoral heterogeneity and/or specific tumour microenvironmental interactions that have hitherto gone unrecognised. We aim to take advantage of cutting-edge single cell-based techniques to deconvolute the tumour- and non-tumour cell architecture of GC, and to identify strategies to modulate these key cellular processes to guide new therapies for children and young adults with this disease. | | |
| **PROJECT AIMS** | | |
| 1. Deconvolution of the cellular environment 2. Validation of GC-specific tumour, immune and normal cell interactions 3. Modulation of cellular interactions to disrupt GC spread and growth | | |
| **RESEARCH PROPOSAL** | | |
| GC is an extensively infiltrating astrocytic glioma involving at least three cerebral lobes, but which preserves normal neural structures. GC frequently involve both cerebral hemispheres, and the widely disseminated nature of the tumour means surgery is rarely an effective option, with a median overall survival of 14.5 months. GC may comprise two distinct groups – "classical" cases without a solid tumor mass, and those which also include a solid tumor portion. This latter group has been reported to harbour *IDH1* R132H mutations, occurring in young adults with a better clinical outcome, whilst little was known about the underlying biology of type 1 GC, which the few previously studied paediatric cases are considered to fall into. Patients with GC are frequently excluded from clinical trials, and therefore represent a serious unmet clinical need.  As a first attempt to study the underlying biology of GC, we have recently participated in the largest collaborative study of GC in young people to date, in association with the International Society of Paediatric Oncology Europe (SIOPE) HGG/DIPG Working Group GC Task Force. Here we assembled 89 new cases in conjunction with previous data across several other studies totalling 133 GCs, with full clinical, radiological and pathological annotation. Although we identified enrichment of GC cases in certain subgroups of the disease (“pedRTK” and “MYCN”), we did not identify fundamental differences in the genetic or epigenetic profiles of GC cases compared to other high grade glioma. These data are currently being finalised in a collaborative manuscript, however the true nature of what causes the specific phenotypes associated with GC remains elusive.  With molecular profiling of bulk GC samples failing to provide insight into what drives these unique tumours, we plan to leverage cutting-edge single cell techniques to deconvolute the architecture of GC and the cells that make up the tumour microenvironment. The proposed PhD studentship will be registered with Prof Chris Jones at the ICR in London, however will form part of a joint project with Dr Mariella Filbin (Dana-Farber Cancer Institute, Boston) and Dr Mara Vinci (Bambino Gesu Hospital, Rome) to take advantage of worldwide expertise in a wide range of techniques which have not been studied in the context of GC previously.  These studies will employ our existing data and sample collections in addition to prospectively collected samples from our respective centres and international collaborators. We will particularly focus on the collection of multi-region samples as well as attempt to generate novel *in vitro* and *in vivo* models of the disease. We will undertake to study the following specific aims:  Deconvolution of the cellular environment  At Prof Jones’s lab, we will employ specific informatic algorithms such as CiberSort and QuanTIseq to our extensive existing methylation or gene expression data of GC to tease out the relative proportions of non-tumour (particularly immune) cells in biopsy samples, and compare these observations with subgroup matched non-GC gliomas. In parallel, Dr Filbin is world-leader in the single cell RNA sequencing (scRNAseq) analysis of paediatric glioma, and will use the established NucSeq and SMARTseq2 platforms from a limited number of frozen (multi-region) GC samples, to identify distinct cell types and cancer cell states. We will also relate this to the tumour genomics by means of inferred chromosomal copy number variations (CNVs) or mutation detection in expressed transcripts. Together this will build up a picture of the cellular hierarchy and heterogeneity of GC in relation to other gliomas, and the relative contribution of the microenvironment to GC biology.  Validation of GC-specific tumour, immune and normal cell interactions  At Dr Vinci’s lab, we will exploit the recent establishment of multiplexed proteomics techniques to validate the observed cell subpopulations predicted from genetic and transcriptomic data. We will utilise single cell mass spectrometry by time-of-flight (scCyTOF) to take key markers identified above to be screened at the proteomic level across large single cell populations to build up a more complete picture of the cellular environment and prioritise key functional regulators of the tumour and non-tumour cell architecture in GC. Moreover, we will use imaging mass cytometry on tissue specimens to assign topographical mapping of these key cell types and states across multiple tumour regions in order to specifically localise the key cellular processes associated with tumour infiltration.  Modulation of cellular interactions to disrupt GC spread and growth  Finally, back in Dr Jones’s lab (with the continued support of Drs Filbin and Vinci), we will utilise novel patient-derived GC models *in vitro* and *in vivo* to functionally assess the prospect of modulating the key players of proposed GC tumour cell-microenvironment interactions. We will employ iterative molecular cell biology experiments focussed on the likely mechanisms underpinning interactions between tumour cell subpopulations and supporting cells. We leverage existing high-throughput and high-content screening approaches aimed at identifying candidate anti-invasion and/or migration compounds that could play a role in disrupting the cellular phenotypes of GC, with the goal of testing such novel approaches in orthotopic xenograft models. | | |
| **LITERATURE REFERENCES** (Please use the Harvard system of referencing and provide up to 10 key references) | | |
| 1. Vinci M, Burford A, Molinari V, Kessler K, Popov S, Clarke M, Taylor KR, Pemberton H, Lord CJ, Gutteridge A, Forshew T, Carvalho D, Marshall LV, Qin EY, Ingram WJ, Moore AS, Ng HK, Trabelsi S, H’mida-Ben Brahim D, Entz-Werle N, Zacharoulis S, Vaidya S, Mandeville HC, Bridges LR, Martin AJ, Al-Sarraj S, Chandler C, Sunol M, Mora J, de Torres C, Cruz O, Carcaboso AM, Monje M, Mackay A and **Jones C** (2018) *“Functional diversity and co-operativity between subclonal populations of paediatric glioblastoma and diffuse intrinsic pontine glioma cells”* Nature Med 24(8):1204-1215 2. Mackay A, Burford A, Molinari V, Jones DTW, Izquierdo E, Brouwer-Visser J, Giangaspero F, Haberler C, Pietsch T, Jacques TS, Figarella-Branger D, Rodriguez D, Morgan PS, Raman P, Waanders AJ, Resnick A, Massimino M, Garre ML, Smith H, Capper D, Pfister SM, Würdinger T, Tam R, Garcia J, Das Thakur M, Vassal G, Jaspan T, Varlet P and **Jones C** (2018) *“Molecular, pathological, radiological and immune profiling of non-brainstem paediatric high grade glioma from the HERBY phase II randomised trial”* Cancer Cell 33(5):829-842 3. Mackay A, Burford A, Carvalho D, Izquierdo E, Fazal Salom J, Taylor K, Bjerke L, Clarke M, Vinci M, Nandhabalan M, Temelso S, Popov S, Molinari V, Raman P, Waanders AJ, Han HJ, Gupta S, Marshall L, Zacharoulis S, Vaidya S, Mandeville HC, Bridges LR, Martin AJ, Al-Sarraj S, Chandler C, Ng HK, Li X, Mu K, Trabelsi S, H’mida Ben-Brahim D, Kisljakov AN, Konovalov DM, Moore AS, Carcaboso AM, Sunol M, de Torres C, Cruz O, Mora J, Shats LI, Bidinotto L, Reis RM, Entz-Werle N, Farrell M, Cryan J, Crimmins D, Caird J, Pears J, Monje M, Debily M-A, Castel D, Grill J, Hawkins C, Nikhbakht H, Jabado N, Baker SJ, Pfister SM, Jones DTW, Fouladi M, von Beueren AO, Baudis M, Resnick A and **Jones C** (2017) *“Integrated molecular meta-analysis of 1000 pediatric high grade glioma and diffuse intrinsic pontine glioma”* Cancer Cell (Johnson et al.) 32(4):520-537 4. Broniscer, A., Chamdine, O., Hwang, S., Lin, T., Pounds, S., Onar-Thomas, A., Shurtleff, S., Allen, S., Gajjar, A., Northcott, P., and Orr, B. A. (2016). Gliomatosis cerebri in children shares molecular characteristics with other pediatric gliomas. Acta Neuropathol *131*, 299-307.   (Broniscer et al., 2016) | | |
| **CANDIDATE PROFILE** | | |
| Note: the ICR’s standard minimum entry requirement is a relevant undergraduate Honours degree (First or 2:1) | | |
| **Pre-requisite qualifications of applicants:**  e.g. BSc or equivalent in specific subject area(s) | | BSc or equivalent in relevant biological science |
| **Intended learning outcomes:**  Please provide a bullet point list (maximum of seven) of the knowledge and skills you expect the student to have attained on completion of the project. | | The successful PhD candidate appointed to this programme will have a unique opportunity to spend time in three outstanding laboratories in the UK, US and Italy, and learn a wide array of cutting-edge laboratory techniques. They will play a central role in European and North American working groups focussed on GC, and present their findings at international GC-specific and more general brain tumour meetings. They will also liaise closely with our funders and other parent groups to communicate the findings of the study, which we hope will provide the platform for novel therapeutic interventions for this currently incurable disease. |
| **ADVERTISING DETAILS** | | |
| **Project suitable for a student with a background in:**  (Please tick all categories that apply – your project will be advertised under all selected categories) | | Biological Sciences  Physics or Engineering  Chemistry  Maths, Statistics or Epidemiology  Computer Science  Other (provide details) |
| **Keywords:**  Please provide 4-6 words/short phrases that potential students may type into search engines (e.g. Google) to search for PhDs similar to yours – e.g. ‘cancer predisposition genes’, ‘physics PhD London’ etc. | | **1.** glioma |
| **2.** invasion |
| **3.** migration |
| **4.** single cell |
| **5.** omics |
| **6.** |
| **FUNDING (only complete this section if this project already has full/partial funding)** | | |
| This project is fully funded | *Full-funding details (this must include stipend, fees and consumables) including the source of funding:*  Rudy Menon Foundation | |
| This project is partly funded | *Part-funding details* (Please set out how much you will provide, from what source, and how much is additionally required; detailing consumables and stipend payments): | |