



Glioma Club16

There were 92 attendees at the seventh 'Glioma Club' arranged by Professor Silvia Marino (Queen Mary University of London) and Professor Paolo Salomoni (University College London) on 28 October 2016 at the National Hospital for Neurology and Neurosurgery, Queen Square, London. This relatively informal symposium is designed for basic researchers, clinician scientists and clinicians working on all aspects of glioma and provides an opportunity to discuss preliminary data, often from ongoing work. The meeting was sponsored by The Brain Tumour Charity, Children with Cancer UK, UCL IQPath, and BNOS.

The keynote speakers were Dr Marcel Kool (German Cancer Research Institute, Heidelberg) and Prof Riccardo Soffietti (University of Turin, Italy).

Dr Kool described nine molecular subgroups amongst what would have been classified histologically as Grade II-III posterior fossa and supratentorial ependymomas although specific genetic mutations have only been identified in three of these subgroups to date. There appears to be clinical correlation, with two subgroups demonstrating poorer outcomes, raising the possibility of treatment de-escalation in the others. Importantly, molecular subtypes are stable during disease progression/relapse (unlike in the case of other gliomas) and they may be associated with different cells of origin. In utero electroporation of some of the gene fusions identified in the subgroups leads to tumour development, and tumours can be serially transplanted.

Prof Soffietti gave a comprehensive review of past and current clinical trials in low grade glioma (LGG) and the hypotheses that remain to be validated. It was thought that full integration of molecular data into clinical trials is challenging and historical data are of limited value until re-analysed using the newly developed WHO classification. Trial design is also problematic in the absence of a validated method of early identification of outcome, due to the long term median survival: in this respect progression-free survival, impact on seizures and PET scanning with aminoacids may prove of utility.

Sotirios Bisdas (UCL and National Hospital for Neurology and Neurosurgery, Queen Square) described use of simultaneous (hybrid) MRI-PET for accurate staging (of particular value in cases where there are indeterminate findings with conventional MRI), differentiation between true progression (recurrence) and pseudo-progression, and as a predictor of outcome, taking though into consideration cost efficiency and workflow issues. In discussion, it was stated that one may rely on advanced MRI techniques in the highly experienced centres but that elsewhere difficulties of standardisation and reproducibility demand the robust (but more expensive) PET.

Stuart Smith (University of Nottingham) updated results with their PLGA/PEG matrix paste for intracavity delivery of chemotherapeutic agents, the objective being to eradicate microscopic deposits at the resection margin, prior to commencement of radiotherapy and with superior contact and controlled release compared with use of wafers. Animal studies have shown that the paste doesn't interfere with scan interpretation, withstands radiotherapy, and is not itself toxic, hydrolysing to water and lactate over a 3-4 month period. A pilot animal study was conducted in the US this summer, showing dramatic improvement in survival, although caution is required in the interpretation of these data at present as the number of animals treated was very small. It is hoped that these animal studies will soon be possible in the UK when other agents eg radio-sensitising PARP inhibitors, and combinations, will be tested. Progress to Phase I human studies should be fast as the paste is FDA-approved for other indications.

Giuseppe Battaglia (UCL) also addressed the topic of drug delivery, although from a chemical approach and preferring the term "somanautics" (which incorporates the concept of autonomous navigation as well as drug delivery). His team synthesises polymersomes which are taken up via endocytosis, disassembling and releasing their contents in low pH conditions, hence with the potential to deliver drugs, genes, proteins, and diagnostics into cells. In the case of astrocytes, it is possible to capitalise on the over-expression of the LDL cholesterol receptor in glial cells; the vesicles self-propel in response to an external gradient of glucose, demonstrating the chemotactic behaviour necessary to achieve sufficient concentrations at required sites.

The enormous heterogeneity seen in glioma is thought to be characterised by neutral evolution within cell populations (Lucy Stead, University of Leeds), clonal expansion having been identified (commonly, if not universally) throughout therapy. Both genetic and phenotypic causes are being explored and functional models of intratumour heterogeneity are being developed.

Sebastian Brandner (UCL and National Hospital for Neurology and Neurosurgery, Queen Square): miR449a has tumour suppressing activity in PNET and glioma mouse models and G protein-coupled receptor 158 (GPR 158) has been identified as one

of eight most likely downstream targets. GPR 158 is highly expressed in the CNS and its expression correlates with survival in The Cancer Genome Atlas (TCGA) patient cohort. It has been found that levels inversely correlate with those of the miRNA in IDH1 mutated human gliomas and oligodendrogliomas but less so with astrocytomas and not at all in glioblastoma multiforme (GBM). It is therefore hypothesised that GPR 158 may be a marker of favourable outcome.

Karin Straathof (UCL) described tumour-specific chimeric antigen receptor (CAR) T cell therapy recently enhanced by co-stimulation to create persistence of effect and lympho-depletion prior to treatment. CAR-T cell production can now be accomplished in 8-10 days (compared with weeks previously) and this has enhanced retention of proliferative capacity. Despite this, no durable responses in gliomas have been reported to date. Hence an immunocompetent murine model which expresses EGFRvIII has been developed and study is suggestive of glioma eradication with additional PD-1 blockade. The challenge remains, though, to identify more commonly present tumour specific antigens (EGFRvIII is not common in paediatric glioma or in many adults).

The programme included the BNOS Junior Forum in which younger members from a range of labs explained their work, the BNOS prize being awarded to John Apps (Barbera group, UCL) for his presentation on molecular profiling of adamantinomatous craniopharyngioma (ACP) which has uncovered a similarity between ACP pathogenesis and amelogenesis during tooth development. The proteomic and phosphoproteomic profiling of meningiomas carried out by Jemma Dunn (Haneman group, Plymouth University) has so far identified three possible therapeutic targets. Isabelle Blomfield (Guillemot group, Crick Institute) is exploring the role of the Id4 protein in regulation of neural stem cell quiescence. Thomas Millner (Marino group, QMUL) described how tumour progression can be visualised by creating optically transparent tissue from opaque organs by the PACT and CLARITY methods; the tissue is stabilised in formalin and acrylamide and then the lipid removed, the procedure requiring fresh tissue and taking 12-16 days. Michael Lewis (Michod group, UCL) reported work to determine the function of the histone chaperone DAXX in the pathogenesis of paediatric glioma and Imran Noorani (Bradley group, University of Cambridge) described the use of transposon-mutagenesis forward genetic screens compared with high-throughput CRISPR-Cas9.

The day finished with a presentation by David Jenkinson, Chief Scientific Officer at The Brain Tumour Charity, who mentioned their new support for a centre treating paediatric LGG, a workshop on biobanking and gave a brief description of new funding for post-docs, junior and senior fellows to be available summer 2017.

Maryanne Roach
November 2016