Glioma Club15

This was the sixth 'Glioma Club' arranged by Professor Silvia Marino (Queen Mary University of London) and Professor Paolo Salomoni (University College London). The relatively informal symposium is designed for basic researchers, clinician scientists and clinicians working on various aspects of the origin, genetics, neuropathology, diagnosis, imaging and treatment of gliomas and provides an opportunity to discuss preliminary data, often from ongoing work. There were 122 attendees at the meeting on 14 October at the National Hospital for Neurology and Neurosurgery, Queen Square, London. The meeting was sponsored by The Brain Tumour Charity, Children with Cancer UK, UCL IQPath, and Essen Bioscience, as well as by BNOS.

The keynote speakers were Prof Richard Gilbertson (Li Ka-shing Chair of Oncology, Head of Department of Oncology and Director of the Cambridge Cancer Centre at Cambridge University) and Prof Federico Calegari (Center for Regenerative Therapies at the Technical University of Dresden).

Prof Gilbertson's team have devised a streamlined path to identify the relevance of the very large chromosomal copy number changes seen in brain tumours such as choroid plexus carcinoma and ependymoma, elucidating which genes within these regions may be drivers of tumourigenesis. This has led to the identification of four totally new potential therapies for ependymoma, with mechanisms of action based on vesicle trafficking and cholesterol biosynthesis. They are being tested in randomised trials in mice in conjunction with surgery and radiotherapy.

Prof Calegari hypotheses that the cell cycle and stemness are two facets of the same coin that co-evolved to play mutually synergistic effects in regulation of neuro/gliogenesis. His work is directed at revealing the role of adult neurogenesis, its place in the ageing process and brain rehabilitation. Whilst not directly relevant to brain tumour pathogenesis at the current stage, it may lead to the future discovery of basic cellular mechanisms potentially translatable to cancer biology.

Steve Pollard (University of Edinburgh) also commented that now that the cataloguing of the genetic disruptions in glioma is nearly completed, the need is for functional studies to elucidate their significance. His work is studying the possible hierarchy between stem cells, progenitor and differentiated cells in glioblastoma multiforme and, in particular, exploring de-differentiation.

Thomas Jacques (UCL/GOSH) reported that cortical dysplasia and tumours are the most common causational factors in children undergoing surgery for epilepsy. Cortical dysplasia cases show loss of cortex architecture and striking "balloon cells" similar to those seen in the genetic disorder, tuberous sclerosis. These cells are packed with mitochondria and lysosomes, and display aberrant mTOR and autophagy pathways, but many complex networks are implicated. His unit is now acting as the coordinating hub for the molecular diagnosis of paediatric embryonal tumours.

The work of Mina Gouti (Crick Institute, about to establish her own lab in Berlin) focuses on the differentiation potential of an elusive type of stem cells called neuromesodermal stem cells that eventually source neurons of the spinal cord and mesodermal cells that form the muscle and bone found adjacent to the spinal cord. This work provides critical insights into a fundamental developmental mechanism underlying tissue specification in the embryo. Alteration of such mechanism could underlie some of the pathologies affecting the spinal cord and adjacent tissues.

Susan Short (University of Leeds) described how RAD51 up-regulation or over-expression in one of the two arms of the DNA repair mechanism (the homologous recombination pathway) may lead to radio-resistance. RAD51 over-expression is bimodal across glioma stem cells and associated with SOX2 expression. Two small molecule inhibitors of RAD51 which appear to be radio-sensitisers are being tested in vivo. Their effect appears to be transient as single agents, however combining them with radiation effectively removes the clonogenic SOX2 cell population.

Florian Siebzehnrubl (University of Cardiff) also addressed the issue of radiosensitivity. His work has shown that slow cycling cells are more radiosensitive but more invasive and tumourigenic. They have increased genomic instability and are chemo-resistant. When cells surviving radiation were sub-cultured, it was found that these rebound cells proliferated rapidly and were very aggressive. Both presenters emphasised the importance of a common and standardised definition of "stem cell".

Andrew McEvoy (National Hospital for Neurology and Neurosurgery) used a well-illustrated and amusing presentation style to introduce scientists to the advances being made in the operating theatre. Today's MRI images are getting closer in definition to

pathology specimens, functional imaging allows for detailed pre-operative planning and discussion with the patient, and operations can be more accurately conducted by robots controlled by a navigation system. As the challenges of tumour heterogeneity and therapy resistance have, to date, resulted in poor results from chemotherapy, efforts must also be directed at these mainstays of treatment: surgery and radiotherapy.

Kevin O'Neill (Imperial NHS Trust) described the iKnife which utilises mass spectrometry to analyse the ionised tissue captured via electro-cautery. The spectra must then be classified against a validated histological database before the iKnife can be used for real-time identification. In contrast, RAMAN lasers are non-destructive and do not require contact being made with the tissue. Once the "noise" due to the infra-red from operating theatre equipment can be counteracted, this technique may be more specific than the iKnife.

Ursula Grazini (UCL Wolfson Institute for Biomedical Research) reported her work on the ruthenium complex, RAP07, identified as a result of a study of Chinese medicine, which inhibits proliferation and migration in vitro. Its use following orthotopic transplantation into immunocompetent mice has shown slowing of tumour growth although, to date, no regression.

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 Giulia Agliardi from the John Anderson Lab, UCL ICH/GOSH for her presentation on preclinical modelling to develop EGFRvIII-targeted T-cell therapy for high grade gliomas. Osama Aldalahmah (Francis Szele Lab, University of Oxford) covered the mechanism of action of galectin-3 in tumourigenesis, James Wood (Richard Grundy Lab, University of Nottingham) discussed sphingolipid and lysophospholipid concentration in the peri-operative invasive margin, and Ying Zhang (Sebastian Bradner Lab, UCL Institute of Neurology) reported on a significant correlation between the expression level of a novel biomarker (a growth factor receptor) and the survival of patients with different types of gliomas.

The day finished with a presentation by Erica Little, Research Manager at The Brain Tumour Charity, who presented the results of the charity's quality of life study, emphasising the very significant deficits and difficulties experienced by large numbers of brain tumour patients.

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