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Quite a large group of low grade brain tumours are caused by mutations in the neurofibromatosis type 2 (NF2 or Merlin) gene. These tumours are schwannomas, 30% of all ependymomas and 60% of all meningiomas. All these tumours can also come as part of familial disease, Neurofibromatosis 2, where these tumours arise in early childhood and in great numbers. Currently there is no effective drug treatment for these tumours. Tumour localisation and multiplicity make surgery and radiosurgery very challenging. The NF2 gene is also affected in some astrocytomas together with other gene defects. Thus, a new therapeutic approach is urgently required for tumours caused by Merlin mutations.

Taking advantage of our direct access to human material from the surgical removal of tumours, we have developed a unique model of primary human cell culture and successfully used it to identify and test new targeted therapies by using 1) drugs which have been tested in early clinical trials in other diseases (thus tolerability and best dose are already known) and using 2) cultures from human tumours. We have then taken a fast track approach which allows drugs to be translated directly into clinic trials for these tumours. We are therefore already undertaking one clinical trial as a result of this approach and have plans for more.

Although this group of low grade tumours is a genetically well-defined group we still found quite a variety of different abnormal signalling pathways and growth factors that are relevant drug targets (1, 2). This would possibly imply that one has to use multiple drugs, which is a potential problem. However, working in collaboration with a group at the Memorial Sloan-Kettering Institute in New York we have discovered a mechanism that accounts for many of the changes in signalling pathways and growth factors occurring in tumour cells with Merlin mutation. Thus we seem to have found a kind of a 'master switch'. More precisely, Merlin interacts and inhibits a protein called Cullin4-Ring E3 Ubiquitin ligase (CRL-DCAF1) that regulates the degradation and activity of many other proteins within the cell. Merlin broadly regulates expression of different key signalling pathways/proteins by inhibiting CRL4-DCAF1 E3 activity. Thus loss of Merlin in these tumours due to mutations results in activation of quite a number of proliferative pathways dependent on CRL4-DCAF1 E3 activity. Thus we have discovered a potentially unifying disease mechanism for these tumours (3, 4) and hypothesize that the CRL4-DCAF1 E3 is a formidable therapeutic target for all Merlin-deficient tumours.

MLN4924, which is a novel first in class specific inhibitor of the activation of a class of proteins incl. CRL4-DCAF1 E3, has recently been developed by Millenium (5). In vitro data derived from

different cancer models show that MLN4924 can reduce proliferation and induce cell death of tumour cells (6). Early clinical trials with MLN4924 determined the maximal tolerated dose and showed a reasonable side effect profile. We hypothesize that MLN4924 has the potential to correct an abnormal master regulator pathway in tumours in which Merlin is lost. Our previous expertise will allow us to test this hypothesis.

Current Research Aims:

1. We will complete our successful research programme to assess the specific role of CRL4-DCAF1-E3 in the development of Merlin-deficient tumours. Specifically we will assess signalling pathways downstream of CRL4-DCAF1 leading to abnormal proliferation, apoptosis and adhesion in human in vitro model of these tumours.
2. We will validate CRL4-DCAF1-E3 as the key therapeutic target and test the novel UPS inhibitor MLN4924 *in vitro* tumour models.
3. We will conduct a feasibility/tolerability study of MLN4924 in a small group of patients.

Applicant: Prof.Oliver Hanemann is a clinical academic running a neuro-oncology clinic with longstanding expertise in basic and clinical research. He is Chair in Clinical Neurobiology and Director of the new Institute of Translational and Stratified Medicine of Plymouth University Peninsula Schools of Medicine and Dentistry. He is also Neurology Lead for neuro-oncology in the Cancer Network South West. Nationally he is elected member of the British Neuro-Oncology Society (BNOS) council, the National Cancer Research Institute (NCRI) Brain Tumour Clinical Studies Group (CSG) and previously NCRI Translational subgroup of Brain Tumour CSG. He is published regularly in high impact journals, has over 100 publications to his name, and his neuro-oncology research is covered by national and international media. His team consists of internationally recognized experts in basic and translational research on a group of so-called "benign" (low grade) brain tumours, which of course are anything but benign for the patients affected.

The team employs laboratory based cell culture models and established the first ever primary human cultures for a specific brain tumour which is now used to test new drugs. In collaboration with a dedicated neuropathologist they also employ tissue from a huge tissue collection in the Neuropathology Department of Plymouth Hospitals NHS Trust (PHNT). The laboratories that Oliver's team works in are in the purpose built, state of the art facilities of the John Bull Building

right next to the PHNT's Derriford Hospital site. Being placed at a Plymouth Medical School and Oliver being a clinical academic running a neuro-oncology clinic (incl. teenage patients) and having expertise in basic and clinical research makes this the ideal basis for making a real change to brain tumour patients.

Costs: Dr Lu Zhou, an experienced postdoctoral researcher who participated in discovering this master mechanism, is funded for the next 24 months, but without the essential support for laboratory consumables this important project cannot be done. Thus Astro Fund will be supplying the funding for laboratory consumables (cell culture media, chemicals, kits) and related support costs, a total of £35.800 over two years.

Papers cited

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