EXECUTIVE SUMMARY

In patient-derived models, targeted inhibition of ACVR1has shown some modest efficacy, suggesting that it may represent a good target for novel drug development. Despite this, little is known about the precise role of mutant ACVR1in DIPG development and/or maintenance, and there is a dearth of available immunocompetent mouse models for biological and preclinical study. Scientific Merit We have used Applied Stem Cell's TARGATT technology to produce founders with site-specific integration of mutant ACVR1and HIST1H3Btransgenes. We plan to combine these established TET-ON HIST1H3B / ACVR1mice with novel CRISPR-basedin uterotumour suppressor gene knockout (e.g. Pten, Bcor) to generate such mouse models of this subtype of the disease. Models will be fully molecularly and phenotypically characterised, with regulable transgenes allowing for assessing the development contexts in which ACVR1and HIST1H3Bmutations interact. Bioluminescent markers are included for assessment of tumour burden in preclinical drug screening experiments. As well as providing novel insights into the role of mutant ACVR1in 6/6/2018 A MOUSE MODEL OF HIST1H3B / ACVR1 MUTANT DIPG

DIPG tumorigenesis, generation of an immunocompetent model of this subgroup ofDIPG will be used for preclinical screening of our ongoing candidate single agent and combination approaches. Feasibility All techniques for breeding and maintenance of genetically engineered mouse models are well established within the ICR's Biological Services Unit and the Centre for Cancer Imaging. Within the Jones lab we have a postdoctoral research fellow with experience and expertise with the in uteroelectroporation protocols from a previous placement at University College London. All CRISPR/Cas9-based techniques are used routinely by numerous members of the lab. With the HIST1H3B / ACVR1transgenic mice already in place, combining with the these gene editing approaches is entirely feasible within the timelines of this grant. Expertise The Jones lab is an international leader in the genomic characterisation of pGBM / DIPG samples, and has published extensively on the molecular profiling of these tumours as well as detailed functional assessment of their defining mutations. We co-discovered the presence of ACVR1 mutations in DIPG and have recently provided the first preclinical assessment of inhibitors directed against the receptor. We form part of the INSTINCT network with Great Ormond Street Hospital and Newcastle University, and the CRUK Children's Brain Tumour Centre of Excellence (with the University of Cambridge), particularly focussed on drug development for high risk paediatric brain tumours. Chris Jones is biology lead on the HERBY and BIOMEDE clinical trials, and former Chair of the Biology Subcommittee of the SIOPE HGG / DIPG Working Group, allowing rapid dissemination of results and clinical translation.