Section 2: Executive Summary

We and others recently discovered a novel cancer gene, *ACVR1*, to be mutated in approximately 25% diffuse intrinsic pontine glioma (DIPG), most commonly in the youngest patients, and co-segregating with K27M mutations in histone H3.1 (*HIST1H3B/HIST1H3C*). *ACVR1* encodes a receptor serine/threonine kinase mutated in the germline of patients with the congenital malformation syndrome FOP (fibrodysplasia ossificans progressiva), and is known to activate the BMP pathway via aberrant responsiveness to activin A and other ligands. As a proof-of-principle to explore the efficacy of targeting the receptor in DIPG, we have utilised a novel series of inhibitors developed by the Structural Genomics Consortium for FOP in our patient-derived models. We have shown a differential efficacy in *ACVR1* mutant DIPGs both *in vitro* and *in vivo* in response to the compounds LDN-193189 and LDN-214117, representing distinct chemotypes, and with concurrent downstream pathway inhibition. Although both compounds penetrate the CNS at doses able to elicit a response, the effects on survival in our orthotopic xenografts remains modest, with an extension of only 14 days. We hypothesis that combining ACVR1 inhibitors with other agents will lead to a prolonged response that may be significantly more likely to prove beneficial to children in the clinic. We propose to identify and test the most effective combinations through rational candidate and screening approaches *in vitro* and *in vivo*. This will be underpinned by our expertise in disease biology and genomics, as well as an innovative analytical approaches to identify novel interactions.