EXECUTIVE SUMMARY

DIPG is the most aggressive of all childhood cancers. It is a type of brain tumor that peaks in incidence at 5-7 years of age and is the most common form of malignant glioma to affect children. There are absolutely no effective treatments and current therapeutic strategies are palliative only. Due to its location within the brainstem, the tumor cannot be removed surgically, it does not respond to chemotherapy, and radiotherapy only slows their growth temporarily. Novel and innovative treatment approaches are therefore urgently needed to counter this tumor. CBL0137 is a novel agent that belongs to a class of anticancer drugs, named “curaxins”, that modulate through transcription, important pathways involved in the development of cancer. CBL0137 directly targets the Facilitates Chromatin Transcription (FACT) complex, a transcription and replication factor composed of the Structure Specific Recognition Protein (SSRP1) and suppressor of Ty 16 (Spt16) proteins. Upon binding of CBL0137, FACT complex is sequestered in the chromatin leading to inhibition of nuclear factor-κB (NF-κB) and activation of TP53. CBL0137 is water soluble, well tolerated and crosses the blood brain barrier. It is currently under evaluation in adult phase I clinical trials for hematological malignancies and solid tumors. Thanks to the work supported by TCSN and the Australian government, A/Prof Ziegler is developing a first-in-child Phase 1 trial of CBL0137 that will open at Children’s Oncology Group (COG) Phase 1 centers with an expansion cohort for DIPG patients across the COG network of > 200 hospitals. Previous experiments performed in our laboratory have shown that CBL0137 is effective against DIPG cells *in vitro* and *in vivo*. CBL0137 affects DIPG cell proliferation through activation of TP53, inhibition of NFkB and, importantly, restores the methylation of H3K27me3. Further analysis has shown that CBL0137 activity can be further enhanced in combination with epigenetic inhibitors panobinostat through further effects on TP53 phosphorylation, enhanced methylation and acetylation in H3K27 and elevated apoptotic markers. Most excitingly and consistent with the *in vitro* results we have found that CBL0137 combined with panobinostat and JQ1 were synergistic in two orthotopic models of DIPG. Furthermore, we have found two additional potent combinations with the poly-ADP ribose polymerase (PARP1) inhibitor olaparib and nuclear factor NFkB inhibitor parthenolide/ACT001. Olaparib is an FDA approved drug for BRCA deficient ovarian cancers. PARP1 has been shown to be overexpressed in DIPG patients' samples. PARP1 modulates the activity of EZH2 methyltransferase, the key enzyme involved histone methylation. Furthermore PARP1 is also found to influence the ability of FACT complex to bind chromatin. Olaparib is currently in phase I/II clinical trials for adult and children patients with Glioblastoma. ACT001 a synthetic analogue of parthenolide is currently under Phase I testing in children with DIPG.

As CBL0137 is now in clinical development as a single agent for children with DIPG it is critical to develop the optimal combination strategy to take to clinical trial. We seek here to build upon our initial findings, and to develop further preclinical evidence required to urgently translate these novel discoveries to clinical trials to directly benefit children with DIPG and other aggressive brain tumors. We aim to determine whether the combination of CBL0137 with olaparib will be effective in DIPG tumors and high-grade gliomas (HGGs). We also intend to evaluate whether the therapeutic efficacy of CBL0137 can be further enhanced with other anticancer drugs such parthenolide/ACT001 which is under clinical evaluation in DIPG patients. In doing so, we aim to develop the quantum of preclinical data required to rapidly translate this therapy from the bench to the bedside for pediatric patients diagnosed with the most aggressive brain tumors. Our team has all the necessary expertise that will ensure the success of the proposed project and ultimately the implementation of the discoveries into the clinic. Dr Maria Tsoli is a senior scientist with particular expertise in DIPG cell cultures and xenograft models, drug combinations and mechanistic studies and has been involved together with A/Prof Ziegler and Dr Ehteda in the co-supervision of a research assistant who has provided the background data described in this project. A/Prof Ziegler has preclinical expertise in pediatric malignant brain tumors and his clinical focus on early phase clinical trials will facilitate translation of positive results to the bedside. The support of A/Prof Ziegler and Prof Haber at Children’s Cancer Institute provides an invaluable environment to ensure the success of this novel research program, and with the ultimate goal of improving outcomes for children diagnosed with DIPG.