PROJECT TITLE

Radiolabeled ALK2 Inhibitors as PET Imaging Agents and a Therapeutic-Enabling Paradigm for the Treatment of Diffuse Intrinsic Pontine Glioma (DIPG)

PRINCIPAL INVESTIGATOR

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SCIENTIFIC SUMMARY

Whole genome sequencing revealed that somatic gain-of-function mutations in activin receptor-like kinase 2 (ALK2), encoded by the ACVR1 gene, are present in ~25–30% of diffuse intrinsic pontine glioma (DIPG) tumors. DIPG, a rare but uniformly fatal pediatric cancer in the pons region of the brainstem, is refractory to radiation treatment (current standard-of-care) and no approved chemotherapeutics currently exist. Encouragingly, pharmacological studies with non-selective kinase inhibitors active against ALK2 demonstrated cell death in lines harboring ALK2 mutations and significant prolongation of progression-free survival in patient-derived xenograft mouse models. These outcomes prompted us to embark on the development of potent and selective ALK2 inhibitors whose safety profile and brain permeability would facilitate a path to the clinic for the treatment of DIPG.

Following an extensive lead generation program conducted as part of a charitable, open science enterprise (partially funded by the OICR CTIP Program), we disclosed three lead compounds with a superior potency, selectivity, and/or blood–brain barrier (BBB) penetration profile versus earlier generation ALK2 inhibitors. Robust in vivo pharmacokinetic (PK) properties and tolerability make these compounds attractive candidates for further optimization, particularly with respect to BBB permeability and distribution into the pons. We felt that positron emission tomography (PET) imaging could serve as a tool to directly visualize and quantify localization of any prospective drug in the brain, so we conducted a study which involved the radiolabeling of our lead compounds with carbon-11 to generate investigational radiotracers. Following administration and brain imaging in healthy rats, it was determined that one of the radiotracers exhibited significant levels of BBB penetration, and more importantly, the compound was distributing into the pons. This marked the first time an agent directed towards the treatment of DIPG was imaged in the clinically relevant area of the brain in a rodent model.

We aim to further expand the use of PET imaging in the lead optimization stage of our ALK2 inhibitor development program by isotopically labelling all advanced leads to evaluate brain permeability and distribution, forming a significant part of our IND-enabling studies. We anticipate that an optimized compound emerging from these studies will be evaluated in an in vivo patient-derived xenograft mouse model of DIPG to satisfy regulatory requirements prior to the initiation of clinical trials. Establishing a suitable radiolabeling strategy that addresses issues of radiotracer metabolism and signal durability is critical to this approach, and the data gathered will inform the parallel development of an optimized PET imaging agent. A PET radiotracer would be invaluable for the clinical development of DIPG therapeutics to confirm target engagement and the pharmacokinetics of binding to brain regions of interest (pons). Ultimately, the aim is for such an agent to aid in patient selection for new clinical trials, determine dosing regimens and assessing effectiveness following implementation of a new therapy. As an ancillary function, we also aim to leverage the PET imaging agents based on our inhibitors to determine whether ALK2 can serve as a suitable biomarker for DIPG, extending their utility to that of non-invasive tools for disease diagnosis.