Docket #: S22-380

A Tyrosine Kinase Inhibitor (TKI) improves downstream signaling of causal genes for Hereditary Hemorrhagic Telangiectasia and Pulmonary Arterial Hypertension and improves endothelial function

The inventors discovered that a known small molecule tyrosine kinase inhibitor may correct the errant signaling pathways in the rare diseases Hereditary Hemorrhagic Telangiectasia (HHT) and Pulmonary Arterial Hypertension (PAH). The compound therefore presents a solution for disease regression and cure, for which an approved solution does not currently exist for neither HHT nor PAH.

HHT is an inherited rare disease that affects roughly 1 in 5,000 people worldwide, and is marked by arteriovenous malformations (AVMs) in the lungs, brain, liver, gastrointestinal tract, nasal mucosa, and skin. These AVMs lead to recurrent nosebleeds in 90% of patients, as well as telangiectasia formation and severe anemia. The inventors show that this TKI targets gene signatures of the disease state, and reverses downstream targets of the errant pathway. It is also shown in an ex vivo endothelial disease model that this TKI inhibits tube formation and proliferation in endothelial cells, suggesting it can also treat HHT by reducing angiogenesis.

Incidence of PAH worldwide is 1 in every 20,000 to 60,000 individuals. Yet, only 15-20% of patients have the inherited form of the disease, caused mainly by loss-of-function mutation in the BMPR2 signaling pathway. In addition, there is evidence that BMPR2 expression and signaling is downregulated in other, non-hereditary forms of PAH as well. Separately from the drug screen for HHT, this same TKI was

also nominated as a treatment for PAH as an activator of the BMP pathway that reverses endothelial dysfunction.

Applications

- Treatment of nosebleeds and severe anemia in HHT patients
- Treatment of AVMs (and therefore a reversal of the disease), especially in the harder to reach GI tract
- Correction of endothelial dysfunction in PAH

Advantages

- A therapeutic approach less invasive than other options such as: ablation, skin grafts, embolization, and nasal closure surgery
- By addressing the underlying disease signaling pathway, this TKI presents a curative option rather than just a treatment of symptoms
- Dual action of treating HHT as both a: 1) VEGF inhibitor; and 2) signaling modulator

Publications

- Md Khadem Ali, Yu Liu, Katharina Schimmel, Nicholas H. Juul, Courtney A. Stockman, Joseph C. Wu, Edda F. Spiekerkoetter. "Identifying transcriptomic downstream targets of genes commonly mutated in Hereditary Hemorrhagic Telangiectasia." bioRxiv 2022.11.26.
- Adam M. Andruska, Md Khadem Ali, Xuefei Tian, Edda Spiekerkoetter. Selective Src-Family B Kinase Inhibition Promotes Pulmonary Artery Endothelial Cell Dysfunction." bioRxiv 2021.09.27.

Patents

- Published Application: WO2024112656

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