MONASH University

Sphingosine kinase 1 targeting agents for the treatment of pulmonary hypertension

THERAPEUTIC: Cardiovascular Diseases

Product Type	Small molecule
Indication / ROA	Pulmonary Hypertension (PH)
Target / MoA	Drug-like (MW < 400Da) sphingosine Kinase 1 (SK1)-proteolysis-targeting agents (SK1-ProTA).
Development Stage	Lead Series (end)
Brief Description & Differentiation	Current approved drugs and clinical candidates for PH only target symptoms (vasodilators). The SK1/S1P signaling axis has been shown to drive PH pathogenesis and disease progression in human patients and preclinical models. Recent preclinical studies involving genetic and pharmacological inhibition of SK1 have validated it as a target for PH: SK1 inhibition reduces vascular remodeling and cardiac hypertrophy. Current SK1 inhibitors suffer from poor bioavailability and selectivity. Our drug-like SK1-ProTA (MW < 400Da) are distinct from other ProTaCs, which are high MW chimeras (MW > 800Da). Nonetheless, they will share the benefits of proteolysis-targeting: improved PK/PD, potential tissue selectivity and higher phenotypic potency. Our orally bioavailable, first-in-class SK1-ProTA agents have demonstrated: • High potency in promoting E3-ligase mediated proteasomal degradation of SK1 (10-100 nM) • Suppression of hypoxia associated vasoconstriction and cardiac hypertrophy • Excellent PK (mice): oral BA (F%) > 50%; $T_{1/2}$ > 8h; Cl_b < 30 mL/min/kg.
Research Team	A/Prof. Bernie Flynn (Monash Institute of Pharmaceutical Sciences); Prof Stuart Pitson (University of South Australia)
Intellectual Property	New compositions of matter, with imminent filing. Monitoring of literature/patent databases did not identify relevant or encumbering documents.
Key Publications	Undisclosed.
Future	Additional *in-vivo* efficacy and safety; lead optimization and candidate selection; CMC.

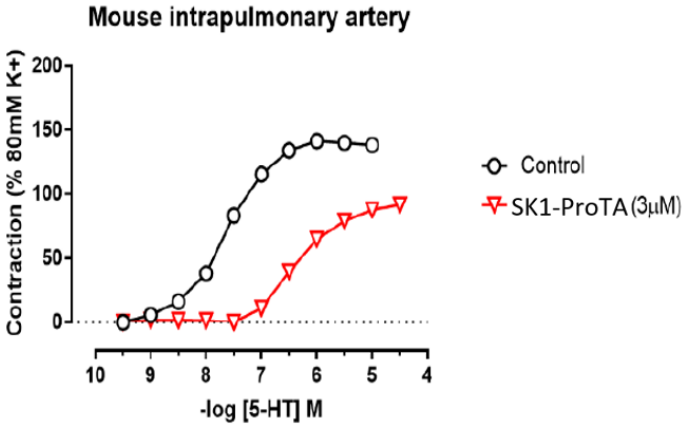

Figure 1 Concentration-dependent contractile response to serotonin 5-HT in the absence (control) and presence of SK1-ProTA (3 µM) lead in mouse isolated intrapulmonary arteries. – Similar Results when using endotherlin-1 (ET-1).

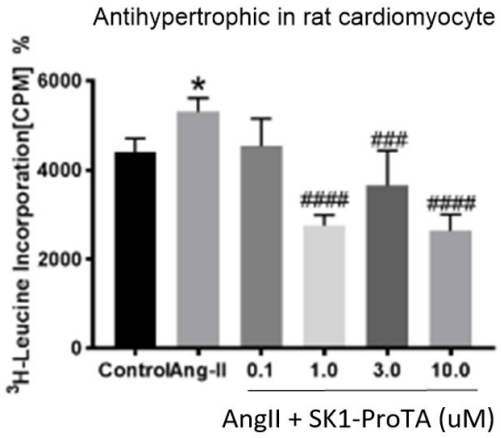

Figure 2 SK1-ProTA inhibits 3H-Leu uptake in AngII stimulated cadiomyocytes (hypertrophy assay).