

## NOVEL SERIES OF 5-HT<sub>1B</sub> ANTAGONISTS FOR TREATMENT OF PULMONARY ARTERIAL HYPERTENSION

Professor Robert Glen and colleagues have developed a novel drug-like series of 5-HT<sub>1B</sub> antagonists with excellent potential for treatment of pulmonary arterial hypertension (PAH) with a low side effect profile and *in-vivo* data showing reversal of PAH.

### Key Features

- Good binding affinity
- Demonstrate reversal of 5-HT<sub>1B</sub> mediated pulmonary vasoconstriction *in-vitro*
- Significant attenuation of hypoxia-induced increases in systolic right ventricular pressure and right ventricular hypertrophy in mouse model of PAH

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## Background

Pulmonary arterial hypertension (PAH) is a life-threatening lung condition whereby patients have elevated blood pressure in the lung which leads to right heart failure and death. PAH is classified into 4 types and is an orphan disease with an estimated patient population of 100,000 in the US & Europe.

Second generation treatments for 3 types of PAH use endothelin antagonists which contain black box warnings due to liver toxicity & potential to damage a fetus.

There is a clear need for safer medicines with a novel and targeted mechanism of action that have a superior side effect profile for treatment across all 4 types of PAH.

Studies have shown the 5-HT<sub>1b</sub> receptor to be involved in the development of PAH in rats & mice exposed to chronic hypoxia. There is therefore strong evidence in the potential of 5-HT<sub>1B</sub> antagonists in the treatment of PAH but whilst many have been developed as research tools, none have the physico-chemical properties for cardiovascular use.

## The Technology

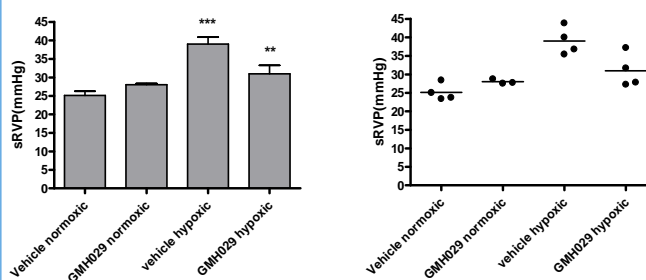
Professor Robert Glen, Dr David Spring, Dr Robin Hiley and their team at the University of Cambridge have generated a novel drug-like series of 5-HT<sub>1B</sub> antagonists with physico-chemical properties consistent with a peripheral vascular treatment. In collaboration with Prof. Mandy MacLean and her team at the University of Glasgow they have generated *in-vivo* data showing reversal of PAH.

## Key Features

- Good binding affinity
- Clear SAR
- Demonstrates reversal of 5-HT<sub>1B</sub> mediated pulmonary vasoconstriction *in-vitro*
- Significant attenuation of hypoxia-induced increases in systolic right ventricular pressure (sRVP) and right ventricular hypertrophy in mouse model of PAH
- no effect on mean systemic arterial pressure or heart rate

- no effect on the increase in contractility to 5HT observed in intralobar pulmonary arteries from hypoxic mice

Figure 1. Mouse model PAH data



The effects of lead compound GMH029 on a chronically hypoxic murine model of PAH were assessed.

Four small groups of  $n=3$  or 4 were used. Mice were dosed either with vehicle ( $dH_2O$ ) or compound at 15mg/kg/day for 14 days whilst being maintained in normoxic (atmospheric pressure) or hypoxic (550mbar) conditions

\*\*\* $p < 0.001$  versus vehicle treated normoxic,

\*\*  $p < 0.01$  versus vehicle treated hypoxic.

The calculated ADMET properties on members of the series are good and satisfy Lipinski's rule of 5 to determine druglikeness. They are stable, contain no reactive functional groups and have log BB values acceptable to lower the transport across the blood brain barrier.

The compounds in this offering demonstrate the profile of a very interesting lead series, with areas for further development identified based on the target product profile and offer a strong basis for development of clinical candidates.

## Commercialisation

We are seeking a commercial partner for licensing, collaboration and development of this technology which is protected by international application number PCT/GB2011/000204 filed on 15th February 2011.