Assessment of cardiac function and pulmonary edema by MRI following pharmacological TRPV4 channel blockade in a murine heart failure model

Hasan Alsaid[1], Stephen C Lenhard[2], Weike Bao[2], Mary V Rambo[3], Alan R Olzinski[2], Gregory A Logan[4], Mark E Burgert[5], James R Tunstead[6], Hilary S Eidam[2], Krista B Goodman[2], Mui Cheung[2], Robert N Willette[2], Kevin S Thorneloe[2], and Beat M Jucker[2,3]

[1]*Preclinical & Translational Imaging, GlaxoSmithKline, King of Prussia, PA, United States,* [2]*Heart Failure DPU, Metabolic Pathways and Cardiovascular Therapy Area Unit,* [3]*Preclinical & Translational Imaging,* [4]*Respiratory Therapy Area Unit,* [5]*Discovery Analytics,* [6]*Platform Technology & Science*

Introduction: Pulmonary edema is a leading cause of hospitalization and mortality in patients with heart failure and is associated with increased pulmonary venous pressure and endothelial barrier dysfunction. TRPV4, a member of the transient receptor potential ion channel family, is highly expressed in alveolar macrophages, the lung endothelium and epithelium. Activation of TRPV4 increases lung permeability, leading to the formation of lung edema (1). GSK2193874A (GSK874A) is a novel TRPV4 channel blocker that inhibits TRPV4 Ca^{2+} flux (*in vitro*, IC_{50} =2 nM). The role of TRPV4 in heart failure induced lung edema remains unknown; therefore we tested whether GSK874A could prevent and/or reverse pulmonary edema and improve pulmonary function assessed by ^{1}H-MRI in a murine heart failure model.

Method: C57BL/6 mice were subjected to ligation of left anterior descending coronary artery to induce myocardial infarction (MI) or to sham surgery. Lung and cardiac MR images were acquired on a 4.7T Bruker magnet to determine lung water signal intensity, lung volume and cardiac ejection fraction. For lung imaging, a 2D FLASH sequence without gating (2) was used to acquire oblique coronal slices and axial slices (7-10 slices covering the entire lung) using the following parameters: TR/TE =6.7/2.2 ms, Flip Angle =10 deg, BW =100KHz, FOV =3X3cm, Matrix =256X128, slice thickness =1 mm, and NEX = 60. For cardiac imaging, an IntraGate Flash sequence was used to acquire long-axis slices and 6 to 9 short-axis slices. Cardiac and lung images were analyzed using Analyze 8.1 AVW software (Analyze Direct, Overland Park, KS). Two pharmacological studies were performed: 1) Preventive study; treatment was initiated 5 days pre-surgery in 3 groups of mice (sham n=8, vehicle n=19 and GSK874A treated n=24 at a dose of 60 mg/kg/day in diet), lung and cardiac MRI were performed at day 14 post surgery (19 days post drug treatment). At the end of the study blood gas analysis and lung wet-weight measurements were performed, and Masson's trichrome staining of the heart was performed to assess the infarct size. 2) Therapeutic study; 3 groups of mice (sham n=6, vehicle n=14, and GSK874A treated n=15 at a dose of 60 mg/kg/day in diet) were imaged at day 7 post surgery (pre-treatment) and at day 14 post surgery (7 days post-treatment). At the end of the study, arterial blood gas analysis and lung wet-weights were measured. Data were presented as Mean ± SEM.

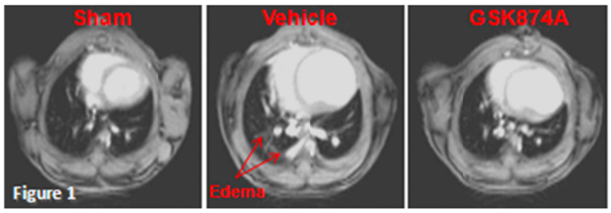

Fig1: Axial lung MR images from the preventive study. The arrows highlight regions of frank edema following MI.

Results: In the preventive study, an approximate increase of 30-35% was observed in lung SI and volume at 2 wks post-MI (Fig 1 & 2a). TRPV4 blockade (GSK874A) reduced significantly lung SI (Fig 2a) and lung volume. This reduction in lung SI was corroborated by a reduction in lung wet-weights as assessed upon necropsy. In addition, there was a significant correlation between total lung SI and wet-weight (Fig 2b). Although there was a significant reduction in left ventricle function following MI, there was no effect of GSK874A on left ventricle ejection fraction or infarct size. In addition, pO_2, and sO_2 were increased significantly with GSK874. In the therapeutic study, a decrease of lung SI was observed at day 14 compared to day 7 in the vehicle group. However, reduction of lung SI (day 14 to day 7) was significantly greater in GSK874A treated group (Fig 2c). Finally, a trend towards improvements were observed in GSK874A treated group with pO_2, sO^2 and lung wet-weight.

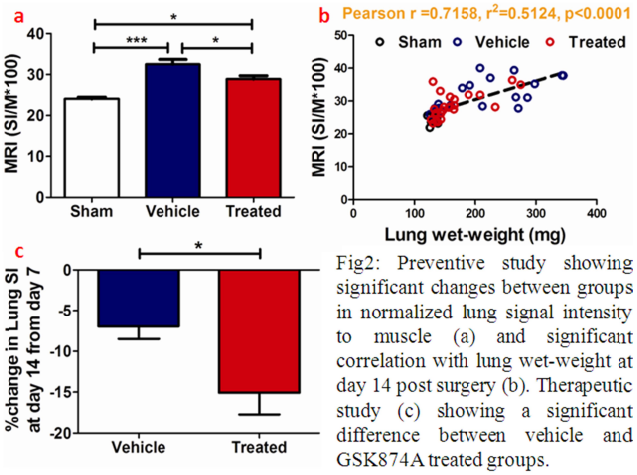

Fig2: Preventive study showing significant changes between groups in normalized lung signal intensity to muscle (a) and significant correlation with lung wet-weight at day 14 post surgery (b). Therapeutic study (c) showing a significant difference between vehicle and GSK874A treated groups.

Conclusion: GSK874A significantly reduced MRI lung water signal intensity, lung volume and edema in a murine heart failure model. GSK874A has no effect on cardiac function and remodeling, indicating that the benefit of GSK874A observed on the lung is independent of its effect on the heart. These results suggest MRI may be used to assess the therapeutic benefit of TRPV4 channel blockade on pulmonary edema in heart failure.

References: (1) Willette R.N et al J. Pharmacol. Exp. Ther, 2008, 326. (2) Alsaid H et al, MRM 2011, doi: 10.1002/mrm.22973.