pulmonary vascular dysfunction in isolated rabbit lungs, acute pulmonary embolism in dogs, acute PH in lambs, monocrotaline (MCT)-induced PH in rats, and chronic hypoxia-induced PH in mice (Stasch and Hobbs 2009; Evgenov et al. 2006; Stasch and Evgenov 2013). The effects of riociguat in these PH animal models are outlined below.

In a mouse model of chronic hypoxia-induced PH, treatment with Riociguat significantly reduced right ventricular systolic pressure (RVSP), ventricular hypertrophy, myocardial fibrosis, and structural remodeling of the lung vasculature (Schermuly et al. 2008). In a rat model of severe PH induced by MCT, which presents with a marked increase in right ventricular systolic pressure, total pulmonary vascular resistance (TPR) and right heart hypertrophy. Riociguat significantly decreased RVSP, TPR, and right heart hypertrophy without a change in systemic arterial pressure (Schermuly et al. 2008). In addition, chronic treatment with riociguat in this rat model resulted in a significant reduction of fully muscularized PAs and increased the percentage of non-muscularized PAs. In another rat model with severe angioproliferative PAH, riociguat significantly decreased RVSP and right ventricular hypertrophy, increased cardiac output, and decreased total pulmonary resistance, compared with vehicle (Lang et al. 2012). Riociguat also significantly decreased the right ventricular collagen content, improved right ventricular function, and significantly lowered the proportion of occluded arteries compared with animals receiving vehicle. In another study, systemic blood pressure increase in a therapeutically relevant low NO/high renin heart failure model (L-NAME-treated renin transgenic rats) was completely prevented and survival was improved by administration of riociguat. Riociguat also reduced cardiac and renal end-organ damage as indicated by lower plasma atrial natriuretic peptide and plasma creatinine and urea levels, respectively, and lowered relative left ventricular weight, cardiac interstitial fibrosis, glomerulosclerosis, and renal interstitial fibrosis. Finally, in salt-sensitive Dahl rats, riociguat markedly attenuated systemic hypertension, improved systolic heart function, increased survival, and ameliorated fibrotic tissue remodeling and degeneration in the heart and kidneys (Stasch and Evgenov 2013).

In phase III clinical trials, riociguat significantly improved pulmonary vascular hemodynamics and increased exercise capacity in patients with PAH and CTEPH (Ghofrani et al. 2013a,b). Furthermore in smaller clinical trials, riociguat improved cardiac output and PVR in patients with PH associated with interstitial lung disease, reduced mean pulmonary arterial pressure (mPAP) and PVR in patients with PH associated with chronic obstructive pulmonary disease, and improved cardiac index and PVR in patients with PH associated with left ventricular dysfunction (Stasch and Evgenov 2013; Bonderman et al. 2013). These promising results suggest that sGC stimulators may constitute a valuable new therapy for PH. Other trials of riociguat are in progress, including long-term extensions of the phase III trials investigating the efficacy and safety of riociguat in patients with PAH and CTEPH (Rubin et al. 2015; Simonneau et al. 2015). Finally, sGC stimulators may also have potential therapeutic applications in other diseases, including heart failure, lung fibrosis, scleroderma, and sickle cell disease.