TENAX THERAPEUTICS

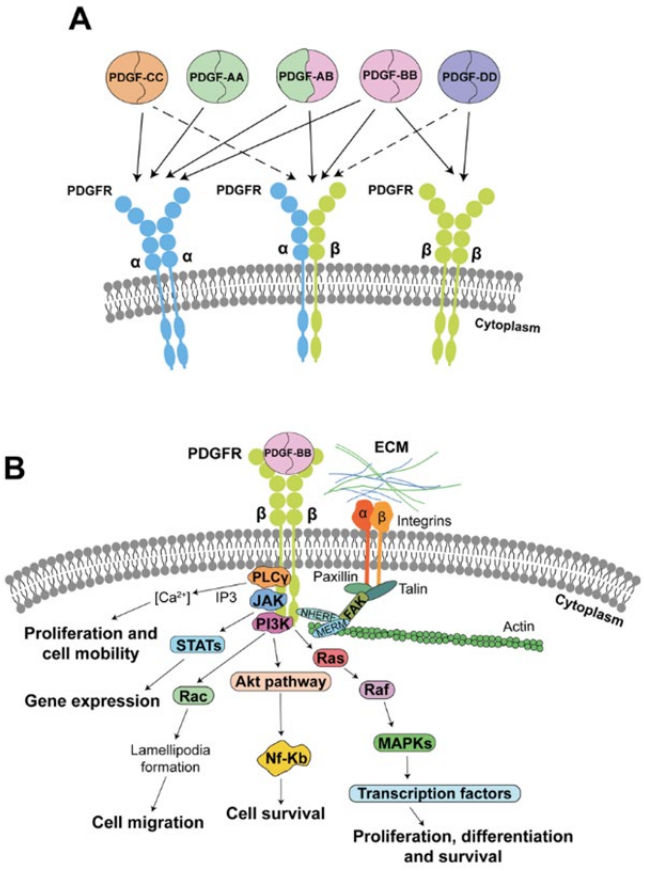
Clinical Evidence to Support Imatinib as a Disease Modifying Treatment for PAH

Robust demonstration of anti-remodeling effects on the pulmonary vascular process in human PAH from any treatment is lacking. The lung pathology of patients with longer survival taking the currently approved PAH therapy shows advanced pulmonary vascular remodeling which supports that these treatments do not halt progression or induce regression of the underlying pulmonary vascular disease. [1,2] In addition, the pulmonary hemodynamics remain extremely abnormal even in those patients with long-term beneficial effects of pulmonary vasodilator treatment, indicating that pulmonary vascular remodeling remains very advanced even in good responders. Thus, it is clear that a treatment that targets the underlying disease process, rather than the hemodynamic abnormalities that it produces, is needed for a treatment to be expected to produce disease reversal and extend survival over the long-term. In summary, given the continued high mortality with current therapy, and the very modest effects on exercise capacity and hemodynamics, it is clear that a new approach to treating PAH is sorely needed.

The initial concept that PAH is largely caused by mechanisms of vasoconstriction has been expanded over the last decades to a more complex picture in which multiple genetic, epigenetic, and environmental mechanisms lead to pulmonary vascular remodeling. [3] In some regards, PAH may even be considered as a pseudo-malignant disease with similar features to cancer, with apoptotic resistance, altered metabolism, and overexpression of growth factor receptors. [4] It is now accepted that curative therapeutic approaches for PAH must address vascular remodeling, by inhibiting proliferative and activating anti-proliferative mechanisms (reverse remodeling). [5]

Many experimental data support the concept that platelet derived growth factor (PDGF) pathways play an important role in the pulmonary vascular remodeling process responsible for the progression of PAH [13,14]. PDGF is known to induce proliferation of pulmonary arterial smooth muscle cells (PASMCs), [Figure 1] and reversal of experimental pulmonary hypertension in the monocrotaline rat model and a hypoxic mouse model was demonstrated with imatinib through PDGF inhibition. [6]

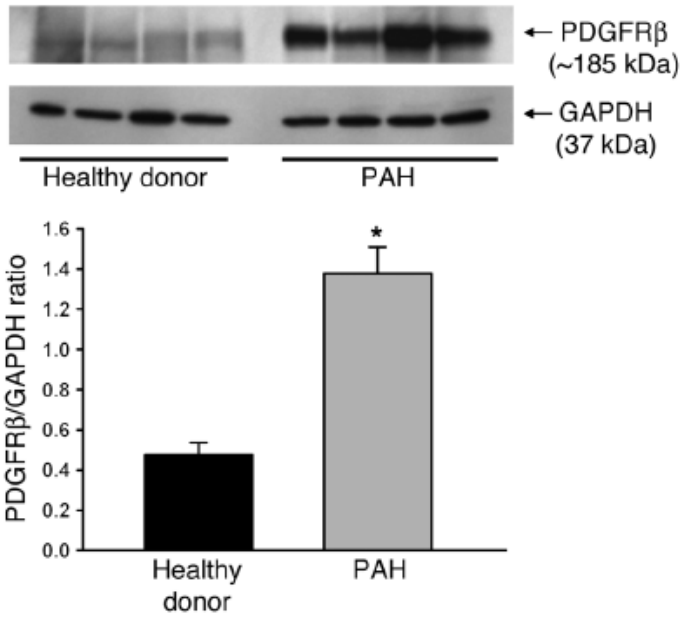
Figure 1



PDGF ligand dimers bind either PDGFRα or PDGFRβ homodimers or the α/β heterodimer. PDGF controls downstream pathways that lead to cellular proliferation and survival. By blocking PDGF receptors, imatinib is able to interfere with those pathways leading to disease reversal (in cancer and PAH).

While animal models of pulmonary hypertension are used to identify promising treatments, they may fail to accurately represent human disease. However, the findings of 1) overexpression of PDGF and PDGFR (receptors) in the pulmonary arterial wall of patients with PAH; 2) the demonstration of PDGF pathway activation in PAH vascular lesions associated with cellular proliferation; and 3) the confirmation of *in vitro* PDGF-induced migration and proliferation of PASMCs, support the hypothesis that PDGF is overexpressed in the pulmonary arteries of human pulmonary hypertensive lungs and is a contributor of pulmonary vascular remodeling in PAH. [7] (Figure 2) Thus, inhibition of PDGF-induced PASMC migration and proliferation with imatinib supports the therapeutic role of PDGF inhibition as a novel approach in PAH. Because PASMC proliferation and migration are believed to be a major contributor to pulmonary vascular remodeling, these findings plead in favor of the potential relevance of PDGF inhibition in the treatment of human PAH.

Figure 2.

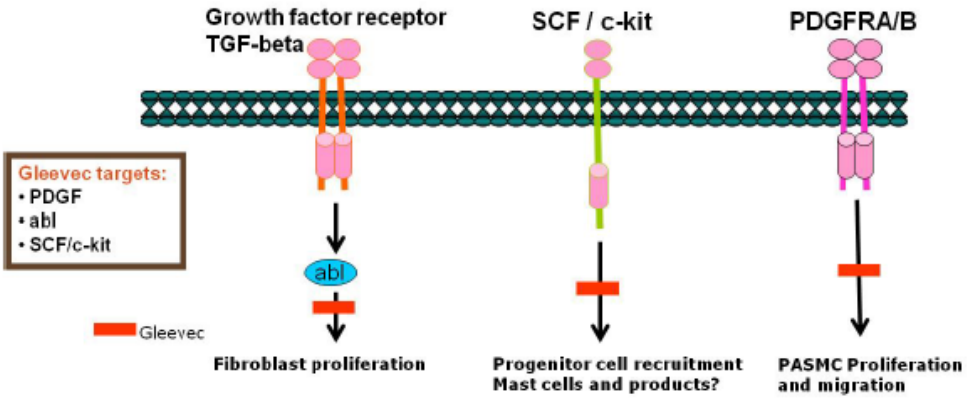


*Change in expression of PDGFRβ in PAH lungs. Expression of PDGFRβ in lung homogenates from patients with PAH (n = 4) and healthy donors (n = 4) and densitometric quantification of the signal intensity. Western blot analysis was performed with anti-PDGFRβ antibody. Quantification of PDGFRβ is shown in the bar graph. *P < 0.05 versus control*

Imatinib mesylate (Gleevec®) is a small molecule tyrosine kinase inhibitor that has been approved for the treatment of various malignant disorders. It is a nonspecific tyrosine kinase inhibitor, interacting with the bcr–abl fusion protein (responsible for efficacy against Ph-positive CML), both α and β PDGFR, DDR, and the c-kit receptor. [8] Pharmacological inhibition of PDGFRs can be achieved by binding and thereby blocking the active site of the phosphate transferring tyrosine kinase. It is a so-called type 2 inhibitor, which binds not only to the ATP binding pocket but also to a site adjacent to the pocket, which enhances specificity and allows binding to the kinase even in an inactive conformation.

Other animal experiments in PH models have shown that imatinib interferes with collagen synthesis in a tryptophan hydroxylase-1 dependent manner,[9] and decreased recruitment of c-KIT+ cells has been reported following imatinib treatment in a chronic hypoxia rat model of pulmonary hypertension. In patients with PAH, imatinib has been shown to inhibit c-KIT+ which was manifested by a reduction in total tryptase, (a marker of mast cell load) in relation to the reduction in pulmonary vascular resistance. [10]

Figure 3.



Given the strength of the preclinical research, Novartis undertook the clinical development of imatinib as a treatment of PAH. Both a phase 2 randomized clinical trial (RCT), [11] and phase 3 RCT [12] were successfully conducted in patients with PAH. The phase 2 pilot study was a double-blinded RCT of imatinib in 59 patients over a 6-month period. The primary end points of this study were safety, tolerability, and change from baseline in 6MWD, with hemodynamics a secondary endpoint. Compared with placebo, there was a non-significant increase in 6MWD. However, there was a significant decrease in pulmonary vascular resistance (PVR) and an increase in cardiac output (CO) with imatinib. The results of this study suggested that imatinib is reasonably well tolerated in patients with PAH and may be efficacious as add-on therapy, particularly in advanced disease.

The phase 3 trial (IMPRES) [12] was a 24-week, multicenter, double-blind, placebo-controlled, parallel-group study. The primary efficacy endpoint was change in 6MWD from baseline to week 24. Secondary efficacy endpoints included changes in pulmonary hemodynamics and time to clinical worsening. A total of 103 patients were randomized to imatinib and 99 to placebo Imatinib significantly improved 6MWD at week 24 compared with placebo, with a mean between-group difference of 32 m (95% CI: 12-52; P=0.002). The study also showed that imatinib resulted in significantly improved hemodynamic parameters. The mean placebo-adjusted improvements in CO and PVR were 0.88 L/min and –4.7 Wood Units (WU) respectively. The magnitude of hemodynamic improvement is notable given that all patients had severe PAH with an average baseline PVR around 15 WU despite already being on multiple PAH treatments. Consistent with the changes in 6MWD, these hemodynamic differences were almost entirely due to improvements in patients randomized to imatinib rather than to deterioration in the placebo group. The IMPRES trial provided strong evidence that imatinib, as the first of a new class of drugs for the treatment of PAH, improves exercise capacity and hemodynamics in patients with

advanced PAH who remain symptomatic on at least 2 drugs of the currently available 4 drug classes.

The problem that was encountered in the IMPRES trial was an overall dropout rate of 33.0% in the imatinib group and 18.4% in the placebo group, giving an excess dropout rate of 14.6% in the imatinib group. The majority of patients who discontinued were from AEs due to gastric intolerance in the imatinib group. This was primarily during the first 8 weeks of treatment, when most imatinib-related AEs occurred.[13] Because of the high dropout rate, the FDA requested a second Phase 3 trial to confirm the efficacy results. Novartis chose to decline and withdrew the NDA.

Currently, treatment with imatinib is the only approach beyond the traditional vasodilator therapy that has shown the potential to offer considerable benefit to PAH patients. Thus, interest in further trials with imatinib and defining those patients with an optimal risk–benefit ratio on the drug remains high.

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