Inhalation of repurposed drugs: A promising strategy for treatment of pulmonary arterial hypertension (PAH)

A brief overview of PAH and various repurposed, inhaled drugs being investigated

Sruthi Sarvepalli, MS; Vineela Parvathaneni, PhD and Vivek Gupta, PhD
St. John's University

Pulmonary arterial hypertension and the need for new therapies

Pulmonary arterial hypertension (PAH) is a rare and progressive disorder characterized by an elevated blood pressure in the pulmonary arterioles [1]. Its features include blockage of the pulmonary arterioles due to defective endothelial function and abnormal proliferation of the pulmonary artery smooth muscle cells and fibroblasts [2]. Consequently, pulmonary arteriole blood pressure increases to > 25 mmHg at rest and > 30 mmHg during physical activity. This clinical definition of PAH has been updated recently to a rise in the pulmonary arterial pressure > 20 mmHg, with normal left atrial pressure and pulmonary vascular resistance ≥ 3 Wood units [2, 3]. PAH is associated with high morbidity and mortality. The major pathological features include pulmonary vascular remodeling and increased pulmonary vascular resistance, which can ultimately result in right ventricular failure and death [4].

According to the World Health Organization (WHO), PAH is classified as Group 1 pulmonary hypertension (PH), which includes a variety of diseases where high blood pressure in the lungs occurs for various reasons; such conditions include idiopathic PAH, heritable PAH and associated PAH [5]. Early symptoms of PAH are very generic, including exertional dyspnea and fatigue. As the disease advances, syncope, chest pain, palpitations and peripheral edema develop. Late-stage PAH patients are at a high risk of right ventricular failure and death [5]. The incidence of PAH is 15 cases per million, based on registry data [6] and the 3-year survival rate is < 60% [7].

Current approved therapies for PAH include prostanoids, endothelin receptor antagonists, phosphodiesterase-5 inhibitors, soluble guanylate cyclase stimulators and other treatments that can provide symptomatic relief by increasing exercise capacity, pulmonary hemodynamics and quality of life. However, none of these provide a cure, as they focus mainly on vascular tone [4, 8]. Moreover, use of these drugs can be limited due to their systemic side effects [9, 10]. Therefore, there is a critical need to discover and develop new drugs targeting vascular remodeling and provide long-term disease reversal benefits. At the same time, for a new drug to reach the market, it must undergo extensive safety and efficacy studies, a time-consuming process that can take approximately 10-15 years. Therefore, drug repurposing, i.e., utilizing an approved drug for a new indication or developing a new administration route for an approved drug, thereby bypassing common challenges of drug discovery, would certainly be beneficial, owing to shorter developmental cycles [11-13].

A rationale for inhaled PAH therapy

Given PAH is a respiratory disorder, access to the large surface area of the lungs provides an important opportunity to target and deliver drugs to the lungs via inhalation (Figure 1). Inhalation as a route of administration for local delivery can offer several desirable features such as therapeutic delivery directly to the target organ (i.e., the lungs) thereby enhancing organ specificity, avoiding first-pass metabolism and reducing systemic side effects. Through inhalation, increased drug concentration at low doses can be achieved at the target site, potentially reducing the

overall dose exposure and/or dosing frequency [14]. Inhalation therapeutics have been studied extensively and results suggest that consistent and reproducible delivery depends on various physiological and biophysical factors such as breathing pattern, lung and airway geometry, particle size (which should be ≤ 5 μm), breath hold following inhalation, etc. These factors can be further classified into drug, formulation, device and patient-related aspects [27]. Due to considerable progress, the inhalation route has become first-line therapy for respiratory diseases such as asthma [28] and chronic obstructive pulmonary disease (COPD).

Inhaled repurposed drugs in PAH clinical trials

Currently, there are more than 160 clinical trials—including 120 completed trials—evaluating approved, novel or repurposed drugs for inhaled administration in the treatment of PAH. Approved drugs include treprostinil while repurposed drugs include nitric oxide and its combination with oxygen, sodium nitrite, imatinib mesylate, albuterol and vardenafil. The majority of the repurposed drugs are being investigated in combination with approved PAH therapies. Further information about some of these drugs is presented here. Clinical trial identifier numbers from https://www.clinicaltrials.gov are noted in the text where applicable [29].

Treprostinil. Treprostinil is a long-acting prostacyclin analog initially developed and approved for intravenous (IV) and subcutaneous infusion in PAH management. Due to systemic side effects with IV administration, researchers developed as an aqueous formulation of treprostinil administered by nebulizer four times per day [30]. (Researchers subsequently developed an oral form of treprostinil and the drug is now is being explored as a liposomal formulation in a Phase I clinical trial (NCT04041648)).

Nitric oxide and its combination with oxygen. Nitric oxide is approved by the FDA for improving oxygenation and reducing the need for extracorporeal membrane oxygenation in neonates with hypoxic respiratory failure associated with PH. Nitric oxide, which is synthesized in the human body by the enzyme nitric oxide synthase [31], is a potent vasodilator. Several clinical trials are investigating its efficacy alone, and in combination with other components such as oxygen, for relieving symptoms of PAH (NCT01092559).

Sodium nitrite. Sodium nitrite is an FDA-approved drug that, due to its vasodilatory effects, is indicated for cyanide poisoning. Based on this, it is under investigation for the inhalation route to treat PAH [32]. In animal models, sodium nitrite has been shown to reduce pulmonary artery pressure [33]. In addition, several completed clinical

Figure 1

Opportunities to repurpose drugs for inhaled delivery in the treatment of PAH

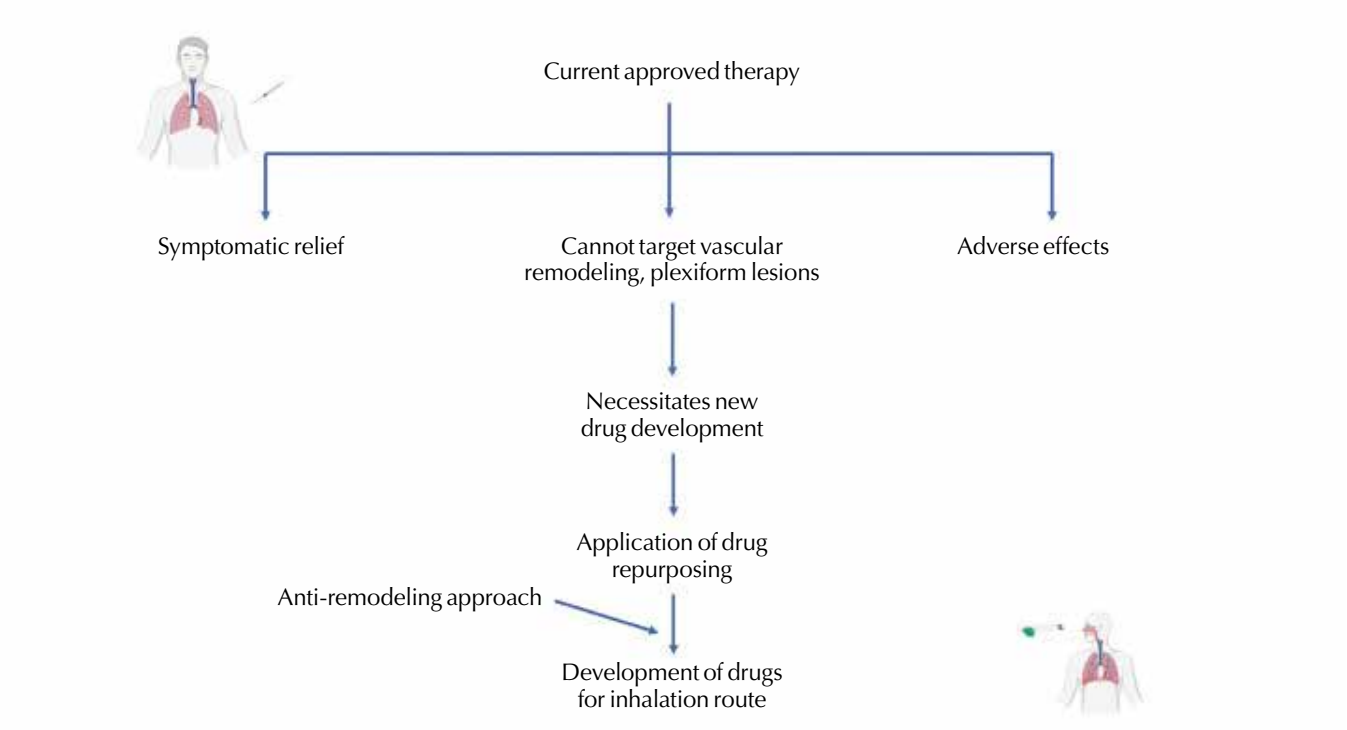
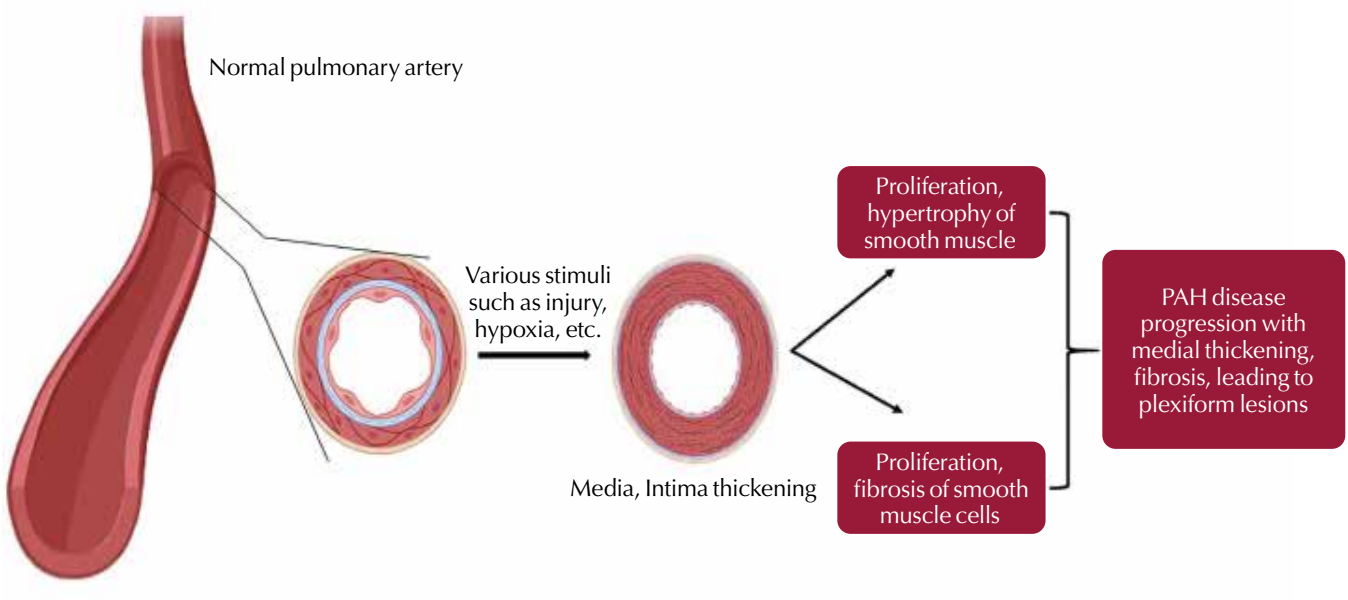


Figure 2

Pulmonary arterial hypertension (PAH) disease and its progression



The Pathology of PAH

As noted earlier, PAH is classified in Group 1 PH, which can be of idiopathic or secondary origins [15]. Irrespective of the root cause, endothelial dysfunction, vascular remodeling, increased vascular resistance and uncontrolled proliferation of smooth muscle cells are the major pathological features of this disease [15, 16].

Broadly speaking, vascular hemodynamics is maintained by three pathways: the nitric oxide (vasodilator), prostacyclin (vasodilator) and endothelin (vasoconstrictor) pathways. Abnormalities in these pathways, due to various causes including autoimmune mechanisms, associated diseases, mutations in the bone morphogenic protein receptor (BMPR2) or unknown causes, can disturb the normal homeostasis of the pulmonary vasculature and may result in enhanced vasoconstrictor activity and suppressed vasodilator activity [17, 18].

Under normal physiological conditions, the tone of the pulmonary arterial walls is maintained by a balance between proliferation and apoptosis of the cells in the tunica intima (endothelial cells), media (smooth muscle cells) and adventitia (fibrotic cells) layers. As PAH progresses and disturbs pulmonary hemodynamics, this balance shifts to favor abnormal- or hyper-proliferation [19-21] of endothelial cells, which leads to endothelial dysfunction in the tunica intima layer. In the next stage, hyperproliferative pulmonary vascular smooth muscle cells (in the tunica media layer) as well as excessive fibrosis (in the tunica adventitia layer) reduce the vascular compliance [22, 23].

The net effect of these events is a hyperplasia phase, including hypertrophy of the intima, media and adventitia of pulmonary arteries/arterioles [22, 24]. Outcomes include vasoconstriction, increased pulmonary arterial pressure, inflammation, obstructive hyperproliferative vascular lesions (vascular remodeling, plexiform lesions), and increased pulmonary vascular resistance.

With the narrowing of the pulmonary arteries/arterioles, the right-sided heart must work hard to pump blood through pulmonary arteries, which leads to cardiac muscle hypertrophy and right ventricle distension. As the disease advances, a set of events including cardiac arrhythmia and right ventricle collapse, can ultimately lead to right-sided heart failure and death. Of these, arrhythmia requires immediate medical attention [18-20].

Pulmonary vascular remodeling and plexiform lesions remain the major pathological features of PAH and often indicate the severity of the disease (Figure 2) [25, 26]. This creates an opportunity to shift the paradigm of therapy from a vasodilatory to an anti-remodeling approach, through the introduction of novel drugs. Involvement of multiple pathological pathways such as inflammation, fibrosis, increased arterial pressure, uncontrolled proliferation and mis-regulated apoptosis, as well as PAH complications beyond the lungs such as reduced exercise capacity, open the door for investigating drug repurposing.

trials concluded sodium nitrite had a beneficial role when administered via inhalation in PAH. Pulmonary vascular impedance analysis in patients using inhaled sodium nitrite showed improved pulmonary vascular compliance through reduction in impedance, which was associated with improved right ventricular efficiency [34]. In addition, the authors tested and confirmed its efficacy in β-thalassemia patients with PH [35].

Imatinib mesylate. With its pathological feature of vascular remodeling, PAH has been identified as a disease with a cancer-like nature and categorized between inflammation and cancer. Imatinib, which is an anti-cancer drug approved as a generic cancer treatment, is the first anti-proliferative agent tested for PAH [36]. In several clinical trials, oral imatinib demonstrated significant efficacy in PAH management. However, it has caused many side effects because of poor tolerability by patients. This has raised researchers' interest in repurposing imatinib for the inhalation route and clinical trials of an inhaled, dry powder aerosol version of imatinib are proceeding. Their premise is that imatinib delivered directly to the lungs could decrease the adverse effects of oral imatinib yet provide benefits to PAH patients [37].

Albuterol. In PAH, compromised exercise capacity is a major concern. The $beta_2$ adrenergic receptor agonist albuterol, which is prescribed for asthma and bronchospasm relief, is being tested via the inhalation route as an add-on therapy for PAH. Studies have also indicated that inhaled albuterol reduces pulmonary vascular resistance in smokers and non-smokers. Based on this, a clinical study examined albuterol effects on hemodynamics of PAH patients. Results showed inhaled albuterol significantly lowered the mean pulmonary arterial pressure and pulmonary vascular resistance for those patients using oral vasodilatory therapy (NCT03270332).

Vardenafil. Vardenafil is a phosphodiesterase-5 inhibitor (PDE5i) and FDA-approved in oral form for erectile dysfunction. While sildenafil, vardenafil and tadalafil act on the same enzyme (PDE-5), these drugs have differences in their pharmacokinetics and selectivity for the enzyme. Vardenafil has 20-fold more potency than sildenafil in PDE-5 inhibition. Based on this, investigators are assessing the ability of a single inhaled dose of vardenafil in PAH patients for improving cardiorespiratory fitness and exercise capacity and reducing dyspnea due to physical exertion (NCT04266197). In addition, in an animal study (a monocrotaline-induced rat model of PAH), vardenafil was shown to reduce oxidative stress [38].

Milrinone. Milrinone is a phosphodiesterase-3 inhibitor (PDE3i) and is approved for cardiac support in patients with acute and chronic heart failure [39]. However, when used in cardiac surgery as an inotrope and vasodilator, intravenous milrinone can cause systemic hypotension. This finding led researchers to conduct an ongoing study comparing inhaled and intravenous milrinone in patients with severe PH undergoing cardiac surgery (NCT04484675). In another clinical trial, the investigators demonstrated that inhaled milrinone reduces pulmonary arterial pressure while supporting desired hemodynamics (NCT01621971). In a third study, researchers quantified the *in vitro* delivery of milrinone using mesh nebulization or jet nebulization; they also measured and compared *in vivo* dosing of milrinone in 12 patients using jet nebulization or mesh nebulization. Results showed that following *in vitro* inhalation using mesh nebulization, the dose was 3-fold higher than with jet nebulization, and after *in vivo* inhalation, the plasma concentration was 2-3 fold higher using mesh nebulization compared to jet nebulization [40]. Further clinical trials are needed to fully establish the milrinone inhalation dosing spectrum as monotherapy or in combination with other approved drugs.

Additional drugs. While several drugs such as allopurinol, metformin, olaparib, dofetilide, famotidine, anakinra, paclitaxel, chloroquine and colchicine are currently under investigation for PAH treatment, paclitaxel is the only drug which is being tested as an aerosol and has shown efficacy by reducing the pulmonary artery smooth muscle cell proliferation and increasing apoptosis [41-43]. Recently, Teymouri Rad, et al. tested and reported increased efficacy of tadalafil nanocomposites when administered as intratracheal insufflation compared to the FDA-approved oral version of tadalafil. Therefore, the authors concluded that inhalable tadalafil nanocomposites could present a promising and an alternative strategy compared to an oral tadalafil in PAH treatment [44].

The need for additional research

Repurposing drugs for inhaled delivery can offer new options in the treatment of PAH. Clinical trials with a variety of inhaled drugs have been completed or are underway. Further research is warranted to establish these repurposed, inhaled drugs for use alone or in combination with existing PAH therapies.

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Sruthi Sarvepalli, MS [Pharm]; Vineela Parvathaneni, PhD; and Vivek Gupta, PhD, Assistant Professor are members of the College of Pharmacy and Health Sciences, St. John's University. Corresponding author: Vivek Gupta, PhD, Assistant Professor, College of Pharmacy and Health Sciences, St. John's University, 8000 Utopia Parkway, Queens, NY, 11439, US. Tel.: +1 718 990-3929, guptav@stjohns.edu, www.guptalabsju.org.

Acknowledgments

This work was supported by startup funds provided to Vivek Gupta by the College of Pharmacy and Health Sciences (CPHS), St. John's University. Sruthi Sarvepalli was supported by a teaching assistantship provided by CPHS, St. John's University.