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Novel Approaches to Pulmonary Arterial Hypertension Drug Discovery

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Abstract

Introduction—Pulmonary arterial hypertension (PAH) is a rare disorder associated with abnormally elevated pulmonary pressures that, if untreated, leads to right heart failure and premature death. The goal of drug development for PAH is to develop effective therapies that halt, or ideally, reverse the obliterative vasculopathy that results in vessel loss and obstruction of blood flow to the lungs.

Areas Covered—This review summarizes the current approach to candidate discovery in PAH and discusses the currently available drug discovery methods that should be implemented to prioritize targets and obtain a comprehensive pharmacological profile of promising compounds with well-defined mechanisms.

Expert opinion—To improve the successful identification of leading drug candidates, it is necessary that traditional pre-clinical studies are combined with drug screening strategies that maximize the characterization of biological activity and identify relevant off-target effects that could hinder the clinical efficacy of the compound when tested in human subjects. A successful drug discovery strategy in PAH will require collaboration of clinician scientists with medicinal chemists and pharmacologists who can identify compounds with an adequate safety profile and biological activity against relevant disease mechanisms.

Keywords

Pulmonary arterial hypertension; high throughput screening; high content imaging; animal models; toxicity; drug discovery; pathology

1. INTRODUCTION

Pulmonary arterial hypertension (PAH) is a life-threatening disorder associated with progressive elevation of pulmonary pressures that leads to right heart failure and death [1].

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With an estimated prevalence of ~15 cases per million patients, PAH is considered a rare disease which often targets women of childbearing age [2]. The diagnosis is based on right heart catheterization measurements and is defined as having a mean pulmonary artery pressure (mPAP) $\geq$ 25 mm Hg, a pulmonary artery wedge pressure of $\leq$ 15 mm Hg, and a pulmonary vascular resistance of $\geq$ 3 Wood units. Prior to the development of PAH-specific therapies, the prognosis of this disease was very poor with a 1-year survival of 69% and a 5-year survival of only 38% [3].

PAH is characterized by remodeling and progressive loss of the small to medium sized pulmonary arterioles with eccentric and obliterative thickening of the intima and media, composed of mainly smooth muscle cells and myofibroblasts. The hallmark of PAH is the plexiform lesion, a disorganized growth of endothelial cells that form false channels that prevent blood flow to the capillaries [4]. Additionally, structural abnormalities such as fragmentation of the elastic lamina, collagen deposition and disorganized extracellular matrix are also seen and likely contribute to the altered properties of the distal pulmonary circulation. [5,6]. The inciting event for these pathological changes is thought to be a combination of genetic and environmental insults that trigger endothelial cell injury. This, coupled with impaired vascular regeneration, leads to progressive loss of small pulmonary arteries [1,7].

Current therapies for PAH are primarily vasodilators that act predominantly on the healthy pulmonary vasculature. They have been shown to improve functional status and survival with an improvement in 1 year survival to 85% and 5 year survival to 57% [8]. However, none of these therapies target the persistent vessel loss and vascular remodeling [9,10], so the disease often progresses leaving lung transplantation as the only treatment option for end-stage PAH [11]. Thus, there is an unmet need for novel therapies that can effectively target the pathological mechanisms driving disease progression and alter the natural history of this devastating disease. This review will describe available strategies used for drug discovery that could facilitate selection of candidate compounds with optimal therapeutic efficacy and minimal toxicity. We believe that these strategies should be incorporated early in drug discovery efforts and would serve as a point of collaboration between academic and pharmaceutical institutions committed to PAH drug discovery.

2. PATHOGENESIS OF PAH

The last two decades have seen a tremendous explosion in the number of discoveries that have provided insight into the genetic, cellular and molecular underpinnings of PAH. In 2000, two independent groups traced the genetic basis of familial PAH to mutations in bone morphogenetic protein receptor 2 (BMPR2), a protein receptor that regulates signaling through the BMP signaling pathway [12,13]. Since then, it has been found that ~80% of familial and 15% of sporadic cases of PAH demonstrate loss of function BMPR2 mutations [14]. Although the penetrance of the mutation is only ~20%, it is still considered a strong risk factor for the development of PAH. Subsequent studies on the role of BMPR2 in the development of PAH have shown that the salutary effect of BMPR2 appears to be mediated by its ability to trigger various downstream signaling pathways including PPAR γ , beta catenin, ERK and p38 among others [15]. Additionally, studies of hereditary PAH in

families without BMPR2 mutations have led to the discovery of other genes that are likely involved in the pathogenesis of PAH. Genes involved in the BMP signaling pathway such as SMAD9 and genes that belong to the TGF family of receptors including ALK-1 and endoglin (ENG) have also been identified in cases of PAH [16–21]. The contribution of these genes to PAH is less well understood but appears to be related to regulation of cell growth and survival in the pulmonary arteries. Recent studies using whole exome sequencing in families with PAH who are BMPR2 mutation negative have identified novel genes such as caveolin-1, TopBP1 and KCNK3 whose biological role in disease pathobiology is currently under study [22–24].

Another significant feature of pulmonary artery endothelial and smooth muscle cells in PAH is a switch from aerobic to anaerobic metabolism, similar to that seen in cancer cells [25,26]. In this setting, transit of acetyl-CoA to the mitochondria is diverted from aerobic metabolism to glycolysis, resulting in suppression of apoptotic cascades and voltage dependent potassium (Kv) channel activity. Derangement of these pathways have been linked to the observed resistance of PAH PSMCs to apoptosis, reduced expression of Kv1.5 and increased cytoplasmic calcium levels which are linked to abnormally increased contractility, hypertrophy and proliferation [27–30].

In addition to the vascular remodeling due to proliferation of PSMCs and transformed endothelial cells, perivascular inflammatory cells are also commonly seen in PAH vascular lesions. These infiltrates are predominantly composed of macrophages, dendritic cells, mast cells and lymphocytes that can appear as disorganized cell clusters or form highly organized pulmonary tertiary lymphoid tissues [4]. Furthermore, circulating levels of specific autoantibodies and inflammatory cytokines that reflect the activation of the innate and adaptive immune systems, have also been shown to be elevated [31,32]. While it is unclear whether inflammation is a trigger or a complication of the vascular pathology, available evidence supports its role as a major modifier of disease progression.

Finally, it must be noted that despite our increasing understanding of the genetic and molecular mechanism behind PAH, it is yet unclear why BMPR2 mutations result exclusively in pulmonary vascular pathology. Given its continuous exposure to the environment, it has been speculated that the lung may have greater susceptibility for environmental factors that could trigger epigenetic changes and other cellular events which would serve as the “second hit” required for disease manifestation. This question is currently the subject of ongoing efforts to identify relevant risk factors involved in PAH pathogenesis and response to therapy.

3. CURRENT THERAPIES FOR MANAGEMENT OF PAH

Prior to the approval of epoprostenol in 1995 [33], there were no specific therapies for PAH and as noted above, survival was very poor. Since then, there has been rapid development of new medications for PAH and now, there are 13 FDA approved PAH specific drugs that have resulted in improved patient outcomes as documented by the U.S. based REVEAL and French Consortium registries[34–37]. These drugs primarily target three pathways: 1) nitric oxide (NO), 2) endothelin and 3) prostacyclins. (Figure 1) It should be noted that some PAH

patients are deemed to be “vasoreactive” and can be treated with calcium channel blockers. These patients fulfill a defined hemodynamic criteria during right heart catheterization, specifically a decrease in mPAP of 10mmHg to below 40mmHg with either a stable or increased cardiac output with exposure to a vasodilator such as inhaled nitric oxide (NO) or adenosine [38,39]. Calcium channel blockers are not recommended for use for patients who do not meet these hemodynamic criteria. For the remaining patients, PAH specific therapies are initiated. Currently, there are five classes of medications that target the three pathways outlined above. In the nitric oxide pathway, L-arginine is converted to L-citrulline in vascular endothelial cells, which leads to the production of NO. Through the activity of soluble guanylate cyclase (sGC), the NO is converted to cGMP that causes to vasodilatation. There are two classes of drugs for PAH in this category: phosphodiesterase-5 inhibitors (PDE-5i) and soluble guanylate cyclase (sGC) stimulators. The PDE-5i prevents the breakdown of cGMP and the sGC stimulators act on sGC to induce increased production of NO. The net effect of both of these drugs is increased concentrations of cGMP that leads to vasodilator. In the endothelin pathway, endothelin produced in endothelial cells binds to receptors on pulmonary artery smooth muscle cells and leads to vasoconstriction. The endothelin receptor antagonists (ERA), bind to the endothelin receptor, thus inhibiting vasoconstriction. Lastly, in the prostacyclin pathway, prostacyclin I₂ (PGI₂) produced by the endothelial cells, binds to the PGI₂ receptor, which leads to the production of cAMP, which then causes vasodilatation. There are now two classes of medications that target this pathway: the prostacyclin analogues and PGI₂ receptor agonists.

The choice of initial therapy is primarily dependent on clinical severity at presentation. The PDE-5i, sGC stimulators, ERAs, and PGI₂ receptor agonists are all oral medications, while the prostacyclins are available in multiple routes of administration including oral, inhaled, and subcutaneous (SQ) and intravenous (IV) continuous infusions. For patients with mild to moderate symptoms, initial therapy with oral medications is appropriate, while IV or SQ prostacyclins should be considered for patients with New York Heart Association (NYHA) functional class 4 symptoms [40,41]. The most recent guidelines recommended sequential addition of drugs that target different pathways to optimize symptoms. However, the recently published AMBITION study has provided evidence that upfront therapy with tadalafil and ambrisentan can confer significant benefit in reducing morbidity and mortality in PAH compared with either tadalafil or ambrisentan alone [42].

On the other hand, despite improving symptoms, quality of life and functional status with currently available therapies, the majority of patients will have progression of their disease. As noted above, it seems likely that the failure of current therapies to reverse or even prevent progression of vascular remodeling or to induce regeneration of lost microvessels explains why patients continue to have progression of their PAH [43]. Furthermore, these therapies should not disable the mechanisms orchestrating right ventricular adaptation as this will result in cardiopulmonary deterioration and may accelerate the appearance of end-stage right heart failure. For this reason, there is an unmet need to seek disease-modifying therapies that can target the cellular component responsible for vascular remodeling in PAH.

4. CURRENT STATE OF DRUG DISCOVERY IN PAH

As we think of novel drugs for PAH, it is imperative that we take into account recent discoveries in the genetics and aberrant signaling pathways that drive cell growth and survival [5,7]. Most studies to date have used a candidate approach to identify genes linked to PAH vascular remodeling by promoting dysregulation of cell growth, survival and matrix production. To test how targeting these candidates with pharmacological or gene therapy approaches can impact vascular pathology, the most commonly used tools have been rodent animal models that recapitulate some but not all of the clinical and pathological hallmarks of the disease [44]. The most commonly used animal models for PAH are rodents exposed to hypoxia, monocrotaline, or SUGEN with hypoxia, but currently there is no perfect preclinical animal model. This remains a major limitation in the capacity to translate therapies to the clinical arena, as most agents that appear to prevent and/or reverse PAH in animals do not necessarily work when administered to humans. This likely reflect different pathobiological mechanisms, inherent differences in the molecular targets unique to the animal model and the unaccounted genetic and environmental complexity of risk factors [45].

Despite these limitations, this approach has yielded some candidate therapies including recently published studies using tyrosine kinase inhibitors such as imatinib [46,47] and recently announced clinical trials such as LARIAT (NCT02036970) and ASK1 (NCT02234141) studies, which use compounds shown in pre-clinical studies to suppress pulmonary artery smooth muscle growth and reverse established vascular remodeling in animal models. Additionally, a phase 1 trial of dichloroacetate (DCA) (NCT01083524), which is a pyruvate dehydrogenase kinase inhibitor that can restore mitochondrial function, was recently completed.

Another potential target for the treatment of PAH is the miRNAs. As discussed above, miRNAs are known to regulate a significant portion of gene expression and a number of these have been implicated in the pathogenesis of PAH. Targeting miRNAs presents a unique opportunity to develop novel therapies for PAH as expression of these molecules can be modulated with antagonists (i.e. antagomirs) that could theoretically be delivered to the pulmonary circulation to alter cell growth and vascular pathology [48]. Despite the abundance of known miRNAs, development of bioinformatic approaches using network analysis has accelerated the identification of miRNAs relevant to the pathobiology of PAH and will likely be able to assist in prioritizing targets for drug discovery [49,50]. Given their critical role in proper cellular maintenance and function, it is likely that miRNA expression is subject to a degree of fine-tuning that can only be understood by use of a network based approach. The interest in miRNAs as novel therapeutic entities is tremendous but is complicated by a number of factors including vector delivery, off-target effects, toxicity, immunological activation and dosage determination. More precise *in silico* approaches and experimental validation to understand miRNA-based disease networks in PH-relevant genes, master effectors, signaling networks, and cell types will allow for the development of miRNA-target therapeutics.

5. NOVEL STRATEGIES FOR DRUG DISCOVERY IN PAH

While the “one gene-one pathway” approach has led to several exciting leads in drug discovery, it must be stressed that cells exist in a dynamic biological environment in which genes interact with other gene networks involved in critical processes that support cellular and tissue homeostasis. Thus, a major drawback of targeting a single gene is potentially deleterious off-target effects that may result in significant toxicity and unacceptable side effects to the patient [51,52]. In addition, reproducibility of results plays a critical role since different conditions across studies can result in inconsistent results and reduce confidence in the compound’s clinical potential. With this background, it is possible to understand the discrepancy between the expenditure for research and development for a lead compound (\$~28–38 million) and the lack of therapies on the market that target new pathways [52]. A comprehensive approach that incorporates screening for toxicity and ensuring proper reproducibility in both cell and animal based models is imperative for accelerating the discovery of compounds with the desired clinical activity [53].

In recent years, there has been increased interest in using bioinformatic approaches for drug discovery. These approaches focus on gene networks involved in cellular processes such as energy metabolism [54], cell survival and proliferation among others [7,55] known to be dysregulated in PAH. Computational methods are relatively fast to implement and accelerate target discovery; however, due to the potentially large data output, this strategy needs to be coupled with a solid bioinformatic analysis platform that can integrate compound–target associations obtained from chemical biology and pharmacological databases [56,57]. In addition to studying candidate molecules for a selected target, this strategy can also be applied to the discovery of novel gene targets that may serve as substrates for drug screening. This ‘genetics-driven genomic drug discovery’ approach is appealing as it can link drug targets with diseased cellular processes and provide a sound rationale for screening specific compounds. This approach has been successful in identifying novel therapeutic targets for rare disorders such as familial hypercholesterolemia (PCSK9) and hereditary xanthinuria (XOR) and perhaps may also be useful for drug discovery for PAH [58–60]. Furthermore, this strategy is also well suited for determining whether existing drugs can be repurposed for treatment of different disorders, an approach that could reduce drug discovery costs and accelerate FDA approval.

The availability of PAH patient derived cells has become a major platform for conducting genetics-driven genomic drug discovery. These cells are isolated from explanted lungs from patients undergoing lung transplantation and can be propagated in culture and banked for future study. At this time, there are ongoing efforts to create national tissue banks such as the Pulmonary Hypertension Breakthrough Initiative and the Cincinnati Children’s Hospital PH Biobank that may be shared with investigators interested in understanding the mechanisms of PAH. Cell models can serve to capture the impact of candidate compounds on genetic suppression or potentiation of specific phenotypes such as cell survival, proliferation or DNA damage. However, it should be noted that there are limitations with this approach. Tissue obtained from patients at the time of lung transplant reflects end stage disease and have likely been exposed to PAH therapies for a number of years. Thus, it is possible that the cellular phenotypes do not reflect the changes that occur during the development of the

disease. Additionally, it is not known how long term therapy may change the phenotype of these cells.

Another approach used by pharmaceutical companies early in drug discovery is high throughput screening (HTS) [61,62]. This strategy leverages mechanical automation to quickly assay the biological or biochemical activity of a large number of drug-like compounds simultaneously under controlled experimental conditions. This technique produces a rapid identification of biologically active compounds with reproducible and reliable readouts. High quality control and hit selection are critical in HTS experiments. This approach was recently employed by Spiekerkoetter et al to screen a library of >3500 FDA approved compounds to identify candidates drugs capable of activating BMPR2 signaling. With this, they identified FK506 (tacrolimus) as a strong activator of BMPR2 [63]. Subsequent studies demonstrated that FK506 reversed PH in an animal model of severe PH by rescuing endothelial dysfunction. Based on these promising results, a phase 2 study (NCT01647945) was recently conducted to test the safety and efficacy of low dose FK506 in patients with PAH [64]. A recent study also used a HTS platform for the discovery of PDLIM5-targeted drugs for PH. The authors identified and validated paclitaxel as a PDLIM5 inhibitor using a stable mink lung epithelial cell line (MLEC) containing a transforming growth factor- β /Smad luciferase reporter. Furthermore, they found that paclitaxel inhibited Smad2 expression and Smad3 phosphorylation in A549 cells [65]. Smad activation is cell type-dependent in pancreatic carcinoma cells, hepatocytes or osteoblasts [66] and results in the induction of Gadd45b and promotes the delayed activation of p38 MAPK. Smad-independent induction of TAK1 leads to rapid, transient p38 activation and has been described in certain cell types including human neutrophils, HEK293 and C2C12 cells. Some mechanisms, such as how Smad7 activates the JNK pathway, remain elusive. While these studies used well-defined targets, knowledge of the target through which the drug works to produce the expected phenotype is not an absolute requirement during initial stages; moreover, attention must be paid to off-target effects related to dosage in an effort to optimize potency and select the best candidate.

The use of a cell-based platform can also be exploited for safety screening using imaging techniques that capture dynamic changes in cellular structure and function. High content imaging (HCI) is a procedure that combines automated microscopy with quantitative image analysis of defined phenotypic (e.g., signal transduction, gene expression, metabolism) or structural (e.g., cell shape, membranes, nuclei, mitochondria) parameters captured with the use of molecular dyes and probes [67–69]. For example, during mitosis, the microtubule based spindle, a cell cycle regulator, ensures the equal division of two daughter cells. Therefore, many cell permeable small molecule drugs can target the spindle in order to modify dynamic cellular processes. However, quantitative assessment of the effects of small molecules and compounds on the spindle function has been rarely used, because methods for automatic recognition of cell phases are not efficient or accurate and manually counting the process is extremely time consuming [70]. The advantage of HCI is that it can capture dynamic changes in multiple biological parameters from the perspective of a single cell or a population exposed to a dose gradient of a candidate compound. The combination of HCI technology with HTS can be a powerful drug discovery tool that provides information about effective drug concentration and associated toxicity.

Another exciting approach to drug discovery in the cardiovascular system is the use of cardiomyocytes differentiated from inducible pluripotent stem cells (iPSC-CM). While the use of iPSC-CM in regenerative medicine is a long-term goal, it does currently serve as an additional tool in drug development. These cells have revolutionized the field of cardiovascular pharmacology by allowing investigators to understand the genetics of inherited cardiovascular disorders and measure the therapeutic index of FDA approved and novel compounds on critical parameters such as myocardial contractility, electrophysiology and cytotoxicity [71,72]. In recent years, efforts have been undertaken to use iPSCs to derive endothelial cells from PAH patient with the goal of further elucidating the genetic and molecular mechanisms of PAH and translating this into a platform for screening novel PAH specific compounds[73]. It should also be noted that this approach can be used to predict the pharmacological profile of a given compound on an individual patient as these cells contain the patient's unique genetic and epigenetic markers. This may be a tool that could predict how different patients might respond to a given compound, supporting the growing movement toward personalized medicine. However, there are major limitations preventing the large-scale use of iPSC-CM in drug discovery and screening, namely inefficient differentiation methodologies and lack of good manufacturing practice standards.

6. SCREENING FOR DRUG TOXICITY

A major determinant of successful drug discovery is selection of agents with minimal toxicity. Monitoring for drug toxicity should be implemented early in the discovery process and maintained beyond drug approval as some toxicities may not be evident in short term studies. This is the focus of medicinal chemistry, a discipline devoted to improving the therapeutic and safety profiles of agents and whose participation in the drug development process can improve the quality of agents tested in clinical studies. Drug modifications that can improve therapeutic index include chemical modifications to the molecular structure to improve solubility and biodistribution as well as designing novel delivery vehicles (e.g. nanocarriers, biogels) to target the drug to the pulmonary vasculature. In addition to the methods described above, there are numerous *in silico* tools such as DEREK, TOPKAT and MCASE that can predict possible toxicity of a given candidate compound by analyzing its molecular structure and comparing it against a database of compounds with similar molecular structures and known toxicity profile [51]. A major benefit of this approach is that structural analysis can help chemists modify the original molecule to improve target selectivity and pharmacological profile while reducing its toxicity.

Another approach for screening for drug toxicity is the use of iPSC-CM cells, as described above. In addition to screening for efficacy of novel compounds, these cells provide a platform to screen the toxicity profile of multiple candidate compounds simultaneously with high throughput technology in cells derived from either circulating blood or skin fibroblasts.

Lastly, it is worth mentioning that animal models of PAH used for preclinical testing of compounds are rarely screened for evidence of possible systemic toxicity for the test compound. Animal models can be used to document and quantify *in vivo* toxicity of candidate compounds by looking at changes in clinical parameters (e.g. behavior, vital signs, EKG) and organ dysfunction through the study of explanted tissues or analysis of

biomarkers in body fluids [51,53]. One must be careful to also consider the toxicity of compounds such as SUGEN and monocrotaline, which are used routinely to induce PAH in rodents and could confound an appropriate assessment of organ damage related to the test compound.

7. CONCLUSIONS

Figure 2 summarizes the proposed flow of drug discovery in PAH. Given the ongoing challenge of caring for PAH patients and the limited therapeutic scope of available therapies, it is necessary to think beyond the current paradigm of using vasodilators and acknowledge the need for disease modifying therapies that tackle the cellular changes driving the vascular pathology of PAH. At present, one of the greatest challenges for treating PAH is the inherent toxicity of available therapies, which can significantly limit treatment success. Drug discovery efforts must be mindful of potential toxicities associated with lead compounds as this can be a significant barrier to translating promising drugs into the clinical setting. The ideal compound should be compatible with existing therapies and significantly reduce the rate of progression while improving quality of life and survival in patients afflicted with this devastating disease.

8. EXPERT OPINION

The field of PAH drug discovery is rapidly undergoing a paradigm shift in which the goal of treatment is to address the vascular pathology responsible for disease progression. To be successful, multidisciplinary approaches combining expertise in computational analysis, genetics, molecular biology, toxicology and medicinal chemistry will be required to identify lead compounds with clinical potential. This will require moving away from a “one-gene-one drug” approach to incorporate the innate complexity of biological systems and account for off-target effects that could compromise the therapeutic properties of lead compounds. Given the immense challenge for discovering clinically relevant and safe drugs, the FDA has established the Critical Path Initiative to assist researchers in both academic and pharmaceutical environments in developing more efficient strategies for drug discovery [74,75].

The future of drug discovery should be based on a “multiple target-multiple drugs” approach where the researcher must take into account the growing knowledge of signaling pathways and gene networks relevant to PAH. This allows the researcher to prioritize relevant targets based on the availability of known protein structures and compound databases that can predict possible pharmacological associations. Even in the absence of such resources, HTS of libraries containing diverse novel and FDA approved compounds can facilitate the discovery of lead compounds capable of restoring gene and protein activity as well as cellular phenotype. It is also worth pointing out that promising *in silico* virtual screening approaches are in development and may serve to narrow the content of libraries to be screened. However, their impact on the drug discovery process will require extensive validation before becoming a part of the drug discovery pipeline.

The drug discovery strategies discussed in this review do not take into account important variables such the pharmacokinetics and pharmacodynamics of compounds. Most compounds will likely undergo first pass metabolism and renal excretion that will determine how much active medication will reach the pulmonary vasculature. This is a major challenge that all drugs face and will determine the route of administration that will guarantee the greatest therapeutic effect for a patient. Thus, while an oral route is generally preferred, we must be prepared to see some of these drugs require inhaled or systemic route for delivery. This will add another layer of complexity, as patients will likely require specialized training to properly take advantage of these therapies. As we have learned from using FDA approved PAH therapies like epoprostenol or treprostinil which require inhaled or systemic delivery, these methods carry the risk complications related to the method of delivery such as infections or interruptions that could severely compromise patient care and result in life-threatening consequences in the absence of proper surveillance and education. Hopefully, innovations in drug delivery systems may alleviate some of these concerns. Current research on drug delivery systems fall into four categories: routes of delivery, delivery vehicles, cargo, and targeting strategies. Drugs can be introduced into the body orally, by inhalation, by absorption through the skin, or by intravenous injection. For example, microneedle arrays can deliver medications through the skin painlessly and are being designed for vaccine delivery. Biodegradable nanoparticles, microparticles or nanosponges that can carry medications to the designated tissue and possibly reduce severe side effects are in development.

In an era of personalized medicine, more space should be given to understanding the heterogeneity of PAH and the underlying drivers. In this way, it might be possible to select the best drug(s) to fit a patient's unique disease phenotype rather than the current empirical approach. This is evident in the recently published AMBITION study, which assumed that all patients who responded to the combination treatment required both drugs; it is worth asking whether patients would have responded to one drug alone before administering both.

Despite the limitations aforementioned, it is imperative that we incorporate these strategies into the current models of drug discovery and take appropriate risks to ensure that new therapies become available to serve our patient population. Success of drug discovery efforts will likely require the collaboration of academic groups and pharmaceutical companies that can pool intellectual and technological resources to assist in this complex process. Ultimately, the final word rests on the capacity to conduct large double blind randomized clinical studies that can effectively capture a treatment response in well-defined PAH patient populations.

References

1. Rubin LJ. Pulmonary arterial hypertension. *Proc Am Thorac Soc.* 2006; 3(1):111–115. [PubMed: 16493158]
- 2**. Galie N, Corris PA, Frost A, Girgis RE, Granton J, Jing ZC, Klepetko W, McGoon MD, McLaughlin VV, Preston IR, Rubin LJ, et al. Updated treatment algorithm of pulmonary arterial hypertension. *Journal of the American College of Cardiology.* 2013; 62(25 Suppl):D60–72. This is the revised algorithm for the treatment of PAH that was drafted at the 5th PAH World

Symposium and illustrates the current approach for choosing a drug class to address functional limitations in PAH patients. [PubMed: 24355643]

3. D'Alonzo GE, Barst RJ, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, Fishman AP, Goldring RM, Groves BM, Kernis JT, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. *Annals of internal medicine*. 1991; 115(5):343–349. [PubMed: 1863023]
- 4*. Stacher E, Graham BB, Hunt JM, Gandjeva A, Groshong SD, McLaughlin VV, Jessup M, Grizzle WE, Aldred MA, Cool CD, Tudor RM. Modern age pathology of pulmonary arterial hypertension. *American journal of respiratory and critical care medicine*. 2012; 186(3):261–272. This study captures the pathological appearance of obliterative vascular lesions in the lungs of PAH patients undergoing transplant and raises important questions regarding the impact of modern therapy on the natural history of PAH. [PubMed: 22679007]
5. Tudor RM, Archer SL, Dorfmueller P, Erzurum SC, Guignabert C, Michelakis E, Rabinovitch M, Schermuly R, Stenmark KR, Morrell NW. Relevant issues in the pathology and pathobiology of pulmonary hypertension. *Journal of the American College of Cardiology*. 2013; 62(25 Suppl):D4–12. [PubMed: 24355640]
6. Rabinovitch M. Pathobiology of pulmonary hypertension. Extracellular matrix. *Clinics in chest medicine*. 2001; 22(3):433–449. viii. [PubMed: 11590839]
- 7**. Rabinovitch M. Molecular pathogenesis of pulmonary arterial hypertension. *The Journal of clinical investigation*. 2012; 122(12):4306–4313. This is a must read state of the art review on the major molecular mechanisms invoked in the pathogenesis of PAH. [PubMed: 23202738]
8. Benza RL, Miller DP, Barst RJ, Badesch DB, Frost AE, McGoon MD. An evaluation of long-term survival from time of diagnosis in pulmonary arterial hypertension from the reveal registry. *Chest*. 2012; 142(2):448–456. [PubMed: 22281797]
9. Enderby CY, Burger C. Medical treatment update on pulmonary arterial hypertension. *Therapeutic advances in chronic disease*. 2015; 6(5):264–272. [PubMed: 26336595]
10. Gazzana MB, Knorst MM. Therapy for pulmonary arterial hypertension: Approved dosages should be prescribed in clinical practice. *Chest*. 2015; 148(4):e126. [PubMed: 26437821]
11. McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, Mathier MA, McGoon MD, Park MH, Rosenson RS, Rubin LJ, et al. Accf/aha 2009 expert consensus document on pulmonary hypertension a report of the american college of cardiology foundation task force on expert consensus documents and the american heart association developed in collaboration with the american college of chest physicians; american thoracic society, inc; and the pulmonary hypertension association. *Journal of the American College of Cardiology*. 2009; 53(17):1573–1619. [PubMed: 19389575]
12. Deng Z, Morse JH, Slager SL, Cuervo N, Moore KJ, Venetos G, Kalachikov S, Cayanis E, Fischer SG, Barst RJ, Hodge SE, et al. Familial primary pulmonary hypertension (gene pph1) is caused by mutations in the bone morphogenetic protein receptor-ii gene. *American journal of human genetics*. 2000; 67(3):737–744. [PubMed: 10903931]
13. International PPHC, Lane KB, Machado RD, Pauciulo MW, Thomson JR, Phillips JA 3rd, Loyd JE, Nichols WC, Trembath RC. Heterozygous germline mutations in *bmpr2*, encoding a *tgf-beta* receptor, cause familial primary pulmonary hypertension. *Nature genetics*. 2000; 26(1):81–84. [PubMed: 10973254]
- 14*. Best DH, Austin ED, Chung WK, Elliott CG. Genetics of pulmonary hypertension. *Current opinion in cardiology*. 2014; 29(6):520–527. Excellent review on the known genetic mutations associated with familial and sporadic forms of PAH with a comment on how these could be targeted with gene therapy. [PubMed: 25159282]
15. Morrell NW. Pulmonary hypertension due to *bmpr2* mutation: A new paradigm for tissue remodeling? *Proc Am Thorac Soc*. 2006; 3(8):680–686. [PubMed: 17065373]
16. Drake KM, Dunmore BJ, McNelly LN, Morrell NW, Aldred MA. Correction of nonsense *bmpr2* and *smad9* mutations by ataluren in pulmonary arterial hypertension. *American journal of respiratory cell and molecular biology*. 2013; 49(3):403–409. [PubMed: 23590310]
17. Drake KM, Zygmunt D, Mavrikakis L, Harbor P, Wang L, Comhair SA, Erzurum SC, Aldred MA. Altered microRNA processing in heritable pulmonary arterial hypertension: An important role for

- smad-8. American journal of respiratory and critical care medicine. 2011; 184(12):1400–1408. [PubMed: 21920918]
18. Nasim MT, Ogo T, Ahmed M, Randall R, Chowdhury HM, Snape KM, Bradshaw TY, Southgate L, Lee GJ, Jackson I, Lord GM, et al. Molecular genetic characterization of smad signaling molecules in pulmonary arterial hypertension. Human mutation. 2011; 32(12):1385–1389. [PubMed: 21898662]
 19. Lenato GM, Guanti G. Hereditary haemorrhagic telangiectasia (hht): Genetic and molecular aspects. Current pharmaceutical design. 2006; 12(10):1173–1193. [PubMed: 16611099]
 20. Newman JH, Trembath RC, Morse JA, Grunig E, Loyd JE, Adnot S, Coccolo F, Ventura C, Phillips JA 3rd, Knowles JA, Janssen B, et al. Genetic basis of pulmonary arterial hypertension: Current understanding and future directions. Journal of the American College of Cardiology. 2004; 43(12 Suppl S):33S–39S. [PubMed: 15194176]
 21. Pousada G, Balloira A, Vilarino C, Cifrian JM, Valverde D. Novel mutations in bmpr2, acvr1 and kcna5 genes and hemodynamic parameters in patients with pulmonary arterial hypertension. PloS one. 2014; 9(6):e100261. [PubMed: 24936649]
 - *22. de Jesus Perez VA, Yuan K, Lyuksyutova MA, Dewey F, Orcholski ME, Shuffle EM, Mathur M, Yancy L Jr, Rojas V, Li CG, Cao A, et al. Whole-exome sequencing reveals topbp1 as a novel gene in idiopathic pulmonary arterial hypertension. American journal of respiratory and critical care medicine. 2014; 189(10):1260–1272. This paper illustrates the use of next generation sequencing strategies to identify candidate genes that could increase susceptibility to PAH. [PubMed: 24702692]
 23. Ma L, Roman-Campos D, Austin ED, Eyries M, Sampson KS, Soubrier F, Germain M, Tregouet DA, Borczuk A, Rosenzweig EB, Girerd B, et al. A novel channelopathy in pulmonary arterial hypertension. The New England journal of medicine. 2013; 369(4):351–361. [PubMed: 23883380]
 24. Austin ED, Ma L, LeDuc C, Berman Rosenzweig E, Borczuk A, Phillips JA 3rd, Palomero T, Sumazin P, Kim HR, Talati MH, West J, et al. Whole exome sequencing to identify a novel gene (caveolin-1) associated with human pulmonary arterial hypertension. Circulation Cardiovascular genetics. 2012; 5(3):336–343. [PubMed: 22474227]
 25. Rehman J, Archer SL. A proposed mitochondrial-metabolic mechanism for initiation and maintenance of pulmonary arterial hypertension in fawn-hooded rats: The warburg model of pulmonary arterial hypertension. Advances in experimental medicine and biology. 2010; 661:171–185. [PubMed: 20204730]
 26. Tudor RM, Davis LA, Graham BB. Targeting energetic metabolism: A new frontier in the pathogenesis and treatment of pulmonary hypertension. American journal of respiratory and critical care medicine. 2012; 185(3):260–266. [PubMed: 22077069]
 27. Bonnet S, Archer SL, Allalunis-Turner J, Haromy A, Beaulieu C, Thompson R, Lee CT, Lopaschuk GD, Puttagunta L, Bonnet S, Harry G, et al. A mitochondria-k⁺ channel axis is suppressed in cancer and its normalization promotes apoptosis and inhibits cancer growth. Cancer cell. 2007; 11(1):37–51. [PubMed: 17222789]
 28. Dromparis P, Sutendra G, Michelakis ED. The role of mitochondria in pulmonary vascular remodeling. Journal of molecular medicine. 2010; 88(10):1003–1010. [PubMed: 20734021]
 29. McMurtry MS, Archer SL, Altieri DC, Bonnet S, Haromy A, Harry G, Bonnet S, Puttagunta L, Michelakis ED. Gene therapy targeting survivin selectively induces pulmonary vascular apoptosis and reverses pulmonary arterial hypertension. The Journal of clinical investigation. 2005; 115(6):1479–1491. [PubMed: 15931388]
 30. McMurtry MS, Bonnet S, Wu X, Dyck JR, Haromy A, Hashimoto K, Michelakis ED. Dichloroacetate prevents and reverses pulmonary hypertension by inducing pulmonary artery smooth muscle cell apoptosis. Circulation research. 2004; 95(8):830–840. [PubMed: 15375007]
 31. Dib H, Tamby MC, Bussone G, Regent A, Berezne A, Lafine C, Broussard C, Simonneau G, Guillemin L, Witko-Sarsat V, Humbert M, et al. Targets of anti-endothelial cell antibodies in pulmonary hypertension and scleroderma. The European respiratory journal. 2012; 39(6):1405–1414. [PubMed: 22005913]
 32. Nicolls MR, Taraseviciene-Stewart L, Rai PR, Badesch DB, Voelkel NF. Autoimmunity and pulmonary hypertension: A perspective. The European respiratory journal. 2005; 26(6):1110–1118. [PubMed: 16319344]

33. Barst RJ, Rubin LJ, Long WA, McGoon MD, Rich S, Badesch DB, Groves BM, Tapson VF, Bourge RC, Brundage BH, Koerner SK, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. *The New England journal of medicine*. 1996; 334(5):296–301. [PubMed: 8532025]
34. Frost AE, Badesch DB, Barst RJ, Benza RL, Elliott CG, Farber HW, Krichman A, Liou TG, Raskob GE, Wason P, Feldkircher K, et al. The changing picture of patients with pulmonary arterial hypertension in the united states: How reveal differs from historic and non-us contemporary registries. *Chest*. 2011; 139(1):128–137. [PubMed: 20558556]
35. McGoon MD, Krichman A, Farber HW, Barst RJ, Raskob GE, Liou TG, Miller DP, Feldkircher K, Giles S. Design of the reveal registry for us patients with pulmonary arterial hypertension. *Mayo Clinic proceedings*. 2008; 83(8):923–931. [PubMed: 18674477]
- *36. McGoon MD, Miller DP. Reveal: A contemporary us pulmonary arterial hypertension registry. *European respiratory review : an official journal of the European Respiratory Society*. 2012; 21(123):8–18. This paper talks about REVEAL, a US based registry that captures demographic and clinical data on WHO group 1 PAH patients receiving modern therapies. [PubMed: 22379169]
37. Humbert M, Sitbon O, Yaici A, Montani D, O'Callaghan DS, Jais X, Parent F, Savale L, Natali D, Gunther S, Chaouat A, et al. Survival in incident and prevalent cohorts of patients with pulmonary arterial hypertension. *The European respiratory journal*. 2010; 36(3):549–555. [PubMed: 20562126]
38. Chaumais MC, Macari EA, Sitbon O. Calcium-channel blockers in pulmonary arterial hypertension. *Handbook of experimental pharmacology*. 2013; 218:161–175. [PubMed: 24092340]
39. Montani D, Savale L, Natali D, Jais X, Herve P, Garcia G, Humbert M, Simonneau G, Sitbon O. Long-term response to calcium-channel blockers in non-idiopathic pulmonary arterial hypertension. *European heart journal*. 2010; 31(15):1898–1907. [PubMed: 20543192]
40. Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, et al. Authors/Task Force M. 2015 esc/ers guidelines for the diagnosis and treatment of pulmonary hypertension: The joint task force for the diagnosis and treatment of pulmonary hypertension of the european society of cardiology (esc) and the european respiratory society (ers) endorsed by: Association for european paediatric and congenital cardiology (aepc), international society for heart and lung transplantation (ishlt). *European heart journal*. 2015
41. Galie N, Simonneau G. The fifth world symposium on pulmonary hypertension. *Journal of the American College of Cardiology*. 2013; 62(25 Suppl):D1–3. [PubMed: 24355633]
42. Galie N, Barbera JA, Frost AE, Ghofrani HA, Hoeper MM, McLaughlin VV, Peacock AJ, Simonneau G, Vachiery JL, Grunig E, Oudiz RJ, et al. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. *The New England journal of medicine*. 2015; 373(9):834–844. [PubMed: 26308684]
43. Gurtu V, Michelakis ED. Emerging therapies and future directions in pulmonary arterial hypertension. *The Canadian journal of cardiology*. 2015; 31(4):489–501. [PubMed: 25840098]
- **44. Ryan JJ, Marsboom G, Archer SL. Rodent models of group 1 pulmonary hypertension. *Handbook of experimental pharmacology*. 2013; 218:105–149. Excellent review on the existing rodent models of PAH that points at their relative strenghts and weaknesses as tools for pre-clinical drug testing. [PubMed: 24092338]
45. Sutendra G, Michelakis ED. Pulmonary arterial hypertension: Challenges in translational research and a vision for change. *Science translational medicine*. 2013; 5(208):208sr205.
46. Frost AE, Barst RJ, Hoeper MM, Chang HJ, Frantz RP, Fukumoto Y, Galie N, Hassoun PM, Klose H, Matsubara H, Morrell NW, et al. Long-term safety and efficacy of imatinib in pulmonary arterial hypertension. *The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation*. 2015; 34(11):1366–1375.
47. Hoeper MM, Barst RJ, Bourge RC, Feldman J, Frost AE, Galie N, Gomez-Sanchez MA, Grimminger F, Grunig E, Hassoun PM, Morrell NW, et al. Imatinib mesylate as add-on therapy for pulmonary arterial hypertension: Results of the randomized impres study. *Circulation*. 2013; 127(10):1128–1138. [PubMed: 23403476]

48. White K, Loscalzo J, Chan SY. Holding our breath: The emerging and anticipated roles of microRNA in pulmonary hypertension. *Pulmonary circulation*. 2012; 2(3):278–290. [PubMed: 23130098]
49. Bertero T, Cottrill K, Krauszman A, Lu Y, Annis S, Hale A, Bhat B, Waxman AB, Chau BN, Kuebler WM, Chan SY. The microRNA-130/301 family controls vasoconstriction in pulmonary hypertension. *The Journal of biological chemistry*. 2015; 290(4):2069–2085. [PubMed: 25505270]
50. Bertero T, Lu Y, Annis S, Hale A, Bhat B, Saggar R, Saggar R, Wallace WD, Ross DJ, Vargas SO, Graham BB, et al. Systems-level regulation of microRNA networks by mir-130/301 promotes pulmonary hypertension. *The Journal of clinical investigation*. 2014; 124(8):3514–3528. [PubMed: 24960162]
- **51. Ahuja V, Sharma S. Drug safety testing paradigm, current progress and future challenges: An overview. *Journal of applied toxicology : JAT*. 2014; 34(6):576–594. This excellent review discusses available strategies for anticipating and establishing drug toxicity in the early development phase. [PubMed: 24777877]
52. Kramer JA, Sagartz JE, Morris DL. The application of discovery toxicology and pathology towards the design of safer pharmaceutical lead candidates. *Nature reviews Drug discovery*. 2007; 6(8):636–649. [PubMed: 17643090]
53. Breyer MD. Improving productivity of modern-day drug discovery. *Expert opinion on drug discovery*. 2014; 9(2):115–118. [PubMed: 24328737]
54. Sutendra G, Michelakis ED. The metabolic basis of pulmonary arterial hypertension. *Cell metabolism*. 2014; 19(4):558–573. [PubMed: 24508506]
55. Geraci MW, Bull TM, Tudor RM. Genomics of pulmonary arterial hypertension: Implications for therapy. *Heart failure clinics*. 2010; 6(1):101–114. [PubMed: 19945066]
- *56. Tseng CY, Tuszynski J. A unified approach to computational drug discovery. *Drug discovery today*. 2015; 20(11):1328–1336. This review provides an introduction to in silico approaches to drug discovery and how these can increase the chances of successfully identifying lead candidates in drug screens. [PubMed: 26189935]
57. Wang RS, Maron BA, Loscalzo J. Systems medicine: Evolution of systems biology from bench to bedside. *Wiley interdisciplinary reviews Systems biology and medicine*. 2015; 7(4):141–161. [PubMed: 25891169]
58. Petrides F, Shearston K, Chatelais M, Guilbaud F, Meilhac O, Lambert G. The promises of pcsk9 inhibition. *Current opinion in lipidology*. 2013; 24(4):307–312. [PubMed: 23817198]
59. Crittenden DB, Pillinger MH. New therapies for gout. *Annual review of medicine*. 2013; 64:325–337.
- **60. Okada Y. From the era of genome analysis to the era of genomic drug discovery: A pioneering example of rheumatoid arthritis. *Clinical genetics*. 2014; 86(5):432–440. This paper uses rheumatoid arthritis as an example of how genomic medicine can assist in the discovery of novel therapeutics for complex disorders. [PubMed: 25060537]
61. Che J, King FJ, Zhou B, Zhou Y. Chemical and biological properties of frequent screening hits. *Journal of chemical information and modeling*. 2012; 52(4):913–926. [PubMed: 22435989]
62. Duffy BC, Zhu L, Decornez H, Kitchen DB. Early phase drug discovery: Cheminformatics and computational techniques in identifying lead series. *Bioorganic & medicinal chemistry*. 2012; 20(18):5324–5342. [PubMed: 22938785]
- *63. Spiekerkoetter E, Tian X, Cai J, Hopper RK, Sudheendra D, Li CG, El-Bizri N, Sawada H, Haghighat R, Chan R, Haghighat L, et al. Fk506 activates bmpr2, rescues endothelial dysfunction, and reverses pulmonary hypertension. *The Journal of clinical investigation*. 2013; 123(8):3600–3613. This paper provides an example of how high throughput drug screening of available FDA approved compound libraries can assist in PAH drug discovery. [PubMed: 23867624]
64. Spiekerkoetter E, Sung YK, Sudheendra D, Bill M, Aldred MA, van de Veerdonk MC, Vonk Noordegraaf A, Long-Boyle J, Dash R, Yang PC, Lawrie A, et al. Low-dose fk506 (tacrolimus) in end-stage pulmonary arterial hypertension. *American journal of respiratory and critical care medicine*. 2015; 192(2):254–257. [PubMed: 26177174]

65. Cheng H, Chen T, Tor M, Park D, Zhou Q, Huang JB, Khatib N, Rong L, Zhou G. A high-throughput screening platform targeting pdlim5 for pulmonary hypertension. *J Biomol Screen*. 2016
66. Takekawa M, Tatebayashi K, Itoh F, Adachi M, Imai K, Saito H. Smad-dependent gadd45beta expression mediates delayed activation of p38 map kinase by tgfbeta. *EMBO J*. 2002; 21(23): 6473–6482. [PubMed: 12456654]
- *67. van Vliet E, Daneshian M, Beilmann M, Davies A, Fava E, Fleck R, Jule Y, Kansy M, Kustermann S, Macko P, Mundy WR, et al. Current approaches and future role of high content imaging in safety sciences and drug discovery. *Altex*. 2014; 31(4):479–493. This paper reviews the major features of high content imaging in the process of identifying the impact of lead compounds on functional cell behavior and toxicity. [PubMed: 25027442]
68. Abraham VC, Taylor DL, Haskins JR. High content screening applied to large-scale cell biology. *Trends in biotechnology*. 2004; 22(1):15–22. [PubMed: 14690618]
69. Persson M, Løye AF, Jacquet M, Mow NS, Thøgersgaard AV, Mow T, Hornberg JJ. High-content analysis/screening for predictive toxicology: Application to hepatotoxicity and genotoxicity. *Basic & clinical pharmacology & toxicology*. 2014; 115(1):18–23. [PubMed: 24461077]
70. Zhou X, Wong STC. High content cellular imaging for drug development. *IEEE Signal Processing Magazine*. 2006:170–174.
71. Burrage PW, Diecke S, Matsa E, Sharma A, Wu H, Wu JC. Modeling cardiovascular diseases with patient-specific human pluripotent stem cell-derived cardiomyocytes. *Methods in molecular biology*. 2016; 1353:119–130. [PubMed: 25690476]
- *72. Ebert AD, Liang P, Wu JC. Induced pluripotent stem cells as a disease modeling and drug screening platform. *Journal of cardiovascular pharmacology*. 2012; 60(4):408–416. This review captures the promising aspects of a drug discovery platform using inducible pluripotent stem cells derived from patient tissue and how it can also aid in early identification of toxicity associated with cardiovascular drugs. [PubMed: 22240913]
73. Geti I, Ormiston ML, Rouhani F, Toshner M, Movassagh M, Nichols J, Mansfield W, Southwood M, Bradley A, Rana AA, Vallier L, et al. A practical and efficient cellular substrate for the generation of induced pluripotent stem cells from adults: Blood-derived endothelial progenitor cells. *Stem cells translational medicine*. 2012; 1(12):855–865. [PubMed: 23283547]
74. Emerging safety science: Workshop summary. Washington (DC): 2008.
- **75. Parekh A, Buckman-Garner S, McCune S, RON, Geanacopoulos M, Amur S, Clingman C, Barratt R, Rocca M, Hills I, Woodcock J. Catalyzing the critical path initiative: FDA's progress in drug development activities. *Clinical pharmacology and therapeutics*. 2015; 97(3):221–233. This document collects the FDA's recommendations for improving drug development success as part of the Critical Path Initiative. [PubMed: 25670629]

ARTICLE HIGHLIGHTS

- Pulmonary arterial hypertension is a life-threatening disease characterized by obstructive vasculopathy of the pulmonary circulation and chronic right heart failure.
- Current therapies for PAH are vasodilators that fail to prevent disease progression.
- Drug discovery in PAH should focus on therapies capable of restoring patency of pulmonary arteries and improving blood flow to the lung.
- Drug screening strategies should be complemented by techniques that monitoring toxicity using available cell based and animal models of PAH.
- Collaboration between academic centers and pharmaceutical industry will likely increase the chance of successful drug discovery.

Figure 1.

Pathways targeted in current therapies for PAH. ERA – endothelin receptor antagonist, NO – nitric oxide, sGC – soluble guanylate cyclase, PDE-5 – phosphodiesterase-5, PDE-5i – phosphodiesterase-5 inhibitor, PGI₂ – prostaglandin I₂, IV – intravenous, INH – inhaled, SQ – subcutaneous

Figure 2.
Diagram summarizing strategies for drug discovery and toxicology profile.