

# Interdisciplinary networks for the treatment of childhood pulmonary vascular disease: what pulmonary hypertension doctors can learn from pediatric oncologists

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**Abstract:** The pathobiology of pulmonary arterial hypertension (PAH) is complex and multifactorial. None of the current therapies has been shown to be universally effective or able to reverse advanced pulmonary vascular disease, characterized by plexiform vascular lesions, or to prevent right ventricular failure in advanced PAH. It is thus unlikely that only one factor, pathway, or gene mutation will explain all forms and cases. Pediatric oncologists recognized a need for intensified, collaborative research within their field more than 40 years ago and implemented major clinical and translational networks worldwide to achieve evidence-based “tailored therapies.” The similarities in the pathobiology (e.g., increased proliferation and resistance to apoptosis in vascular cells and perivascular inflammation) and the uncertainties in the proper treatment of both cancer and pulmonary hypertension (PH) have led to the idea of building interdisciplinary networks among PH centers to achieve rapid translation of basic research findings, optimal diagnostic algorithms, and significant, sustained treatment results. Such networks leading to patient registries, clinical trials, drug development, and innovative, effective therapies are urgently needed for the care of children with PH. This article reviews the current status, limitations, and recent developments in the field of pediatric PH. It is suggested that the oncologists’ exemplary networks, concepts, and results in the treatment of acute lymphoblastic leukemia are applicable to future networks and innovative therapies for pediatric pulmonary hypertensive vascular disease and right ventricular dysfunction.

**Keywords:** pulmonary hypertension, vascular disease, network, clinical trial, children, neonates.

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## INTRODUCTION

Pulmonary vascular disease (PVD) is characterized by progressive obliteration of pulmonary arterioles, leading to increased pulmonary vascular resistance (PVR), right heart failure, and death in  $\approx 32\%$ – $66\%$  of pulmonary arterial hypertension (PAH) patients 5 years after diagnosis.<sup>1</sup> Untreated idiopathic PAH results in death within 2–3 years in adults and within 1 year after diagnosis in children.<sup>2</sup> In the preepoprostenol era (approval in 1995), the prognosis for children treated for idiopathic PAH was poorer than that for adults, with a median survival of only 10 months versus 2.8 years, according to the National Institutes of Health (NIH) registry. On the basis of a more recent UK cohort study (1986 and 2000; follow-up to 2007), survival for children with idiopathic PAH 5 years after diagnosis

is still only  $\approx 75\%$  (vs. historical controls), with a freedom from death or transplantation of only 57%.<sup>3</sup> The outcome with lung or heart and lung transplantation is also far from ideal, with a 5-year posttransplant survival of  $\approx 45\%$ .

PAH is a rare disease, with an estimated prevalence of 15–50 cases per million adults<sup>4,5</sup> and 2–16 cases per million children.<sup>3,6,7</sup> More precisely, the estimated incidence and prevalence of idiopathic PAH was 0.48 and 2.1, respectively, per million children in the United Kingdom.<sup>3</sup> In the Netherlands, the incidence and prevalence of idiopathic PAH was 0.7 and 4.4 per million children, whereas PAH associated with congenital heart disease had an incidence of 2.2 and a prevalence of 15.6 per million.<sup>7</sup> However, in certain at-risk groups the frequency of PAH is

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substantially higher. For example, the prevalence is 0.5% in HIV-infected patients<sup>8</sup> and  $\approx 16\%$  in those with systemic sclerosis. Of note, diseases resembling a substantially increased risk for pulmonary hypertensive vascular disease (PHVD), such as schistosomiasis, HIV, and untreated congenital or acquired heart disease, are far more common in developing countries with limited health care, and hence the true global burden of PHVD is widely underestimated.<sup>9</sup> Moreover, it was demonstrated that conditions that are associated with the “metabolic syndrome” in the developed world, such as insulin resistance and dyslipidemia (here: low high-density lipoprotein [HDL] cholesterol, HDL-C), represent previously unrecognized PAH risk factors or disease modifiers.<sup>10</sup> In 2009, the presence of both insulin resistance and dyslipidemia was shown to be associated with worse clinical outcome, including survival after 6 months of follow-up.<sup>10</sup> Subsequently, Heresi et al.<sup>11</sup> confirmed the inverse relationship between low plasma HDL-C levels and combined PAH end points and survival after 2 years of follow-up. On the basis of the epidemic “metabolic syndrome” in North America and Europe, these observations raise concerns that the incidence of PAH (currently 2.4–7.6 cases per million adults annually in France<sup>4</sup> and Scotland<sup>5</sup> and 0.5–2.2 cases per million children annually in the United Kingdom<sup>3</sup> and the Netherlands<sup>7</sup>) will increase significantly over the next two decades.

*Similarities between advanced PAH and cancer.* The pathobiology of PAH is complex and multifactorial (reviewed in Michelakis et al.,<sup>12</sup> Rabinovitch,<sup>13</sup> Rhodes et al.,<sup>14</sup> Hansmann and Zamanian,<sup>15</sup> Hansmann,<sup>16</sup> and Archer et al.<sup>17</sup>), and none of the current therapies has been shown to be universally effective or able to reverse advanced PVD, characterized by plexiform vascular lesions.<sup>1,18,19</sup> Thus, it is unlikely that only one factor, pathway, or gene mutation will explain all forms and cases. This underscores that both basic scientists and clinicians need to address several molecular pathways as well as genetic and environmental modifiers of PAH. Pediatric oncologists recognized such a need for intensified, collaborative research within their field more than 40 years ago and implemented major clinical and translational networks worldwide. The similarities in the pathobiology (e.g., increased proliferation and resistance to apoptosis in vascular cells and perivascular inflammation<sup>12,20,21</sup>) and the uncertainties in the proper treatment of both cancer and PAH<sup>19</sup> have led to the idea of building clinical networks among PAH centers to achieve optimal diagnostic algorithms and significant and sustained treatment results. Such networks leading to a unified patient

registry, clinical trials, optimal diagnostic algorithms, drug development, and innovative effective therapies are urgently needed for the clinical care of children with PAH.<sup>22</sup>

This article reviews the current status, limitations, and recent developments in the field of pediatric pulmonary hypertension (PH). It is suggested that the oncologists’ exemplary networks, concepts, and results in the treatment of acute lymphoblastic leukemia (ALL) may be applicable to future expert networks and innovative therapies for pediatric PHVD (PPHVD) and right ventricular dysfunction (RVD).

### ESTABLISHMENT OF CLINICAL NETWORKS IN PEDIATRIC ONCOLOGY: THE ALL SUCCESS STORY

Treatment of ALL is one of the true success stories of modern oncology. During the last 50 years, ALL has gone from a uniformly fatal disease to an illness with an overall cure rate of 75%–80%. The clinical success was based on strong bench research in drug development, the idea of multiple drug therapy, and cooperative clinical trials among multiple centers of excellence: combinatory chemotherapy for cancer was suggested in 1965 by Emil Frei, Emil Freireich, and James Holland. They envisioned that each of the drugs used should have a different mechanism of action since cancer cells frequently undergo mutations and become resistant to a single agent.

Major clinical networks investigating combination chemotherapy for ALL and other forms of cancer were established in the 1970s. These included (1) the BFM (Berlin-Frankfurt-Münster) Study Group (ALL-BFM protocols, Germany), (2) the Leukemia Steering Committee of the Medical Research Council in the United Kingdom (UKALL), and (3) the Pediatric Oncology Group (United States, Canada).

In 1968, Donald Pinkel (Memphis) presented his treatment results for children with ALL in Munich, and 6 years later nearly identical results were achieved in the first cooperative trial for treating ALL in Germany (i.e., the BFM Study Group, founded 1976 by Hansjörg Riehm). Today, pediatric oncologists in more than 70 hospitals throughout Germany, Austria, and Switzerland participate in this cooperation (e.g., the ALL-BFM 2000 trial). Consequently, more than 90% of children with hematologic-oncologic diseases living in one of these three countries or the United Kingdom<sup>23</sup> (e.g., the UKALL 2003 trial) are being centrally registered and subsequently enrolled into clinical trials.

In 2000, the Pediatric Oncology Group, consisting of more than 100 centers in the United States and Canada, merged with the Children’s Cancer Study Group, the Intergroup Rhabdomyosarcoma Study Group, and the Na-

tional Wilms Tumor Study Group to form the Children's Oncology Group, an international clinical trial cooperative group supported by the National Cancer Institute. During the last few years, many therapy-optimizing randomized controlled trials (RCTs) of ALL have been conducted in Europe, North America, and even worldwide and have led to impressive survival rates in children with ALL.

*How was that achieved?* Apart from the important patient registries, a common concept of both the European and the North American oncology networks is that leading study centers are established in large academic institutions throughout the network but that smaller community-level centers are encouraged to contribute and have their patients enrolled in a suitable, centrally managed trial. The advantages of having one "trial-leading center" for each trial but more than one such "prime center" in the network are evident in the more reasonable workload for each of those centers and their ability to focus on a particular disease subtype or disease state (e.g., first presentation, remission, or relapse) while gaining further clinical and scientific expertise.

## WHAT CAN PH DOCTORS LEARN FROM PEDIATRIC ONCOLOGISTS?

### 1. Aim to centrally register every patient with PVD

The goal would be to build one international registry (instead of various databases that will be difficult to integrate later on), which will help unifying investigators to foster collaboration and the clinical care of children with PH.<sup>24</sup> While building a large collaborative PVD network and patient registry for children in the near future, close collaboration with adult PH centers and networks is highly desirable to utilize broader resources and experience, thereby improving the translation of basic science and novel concepts into clinical practice. Such an international collaborative group could be, for example, supported by the National Heart, Lung, and Blood Institute (NHLBI),<sup>25</sup> the European Research Council, and other international private and federal nonprofit funding agencies.

*Are we there yet?* The exemplary Pulmonary Hypertension Breakthrough Initiative Research Network, sponsored by the Cardiovascular Medical Research and Education Fund, is a collaborative group of multidisciplinary transplant and research centers exploring the etiology and pathogenesis of familial and idiopathic PAH. A databank/coordinating center has been established and is responsible for the design, maintenance, and analysis of the PAH database. The studies range from molecular to clinical projects in the fields of pharmacology, physiology, genetics, genomics, medicine, surgery, epidemiology, statistics, bio-

informatics, and computational biology. Moreover, several task forces established by the Pulmonary Vascular Research Institute (PVRI) aim to facilitate rapid and comprehensive communication and knowledge exchange among basic scientists and clinicians working in the field of PAH. It is encouraging that the US-based Pulmonary Hypertension Association—driven by patients and healthcare providers—collaborates with similar associations around the world and the PVRI.

*PH patient registries.* The REVEAL Registry (Registry to Evaluate Early and Long-Term PAH Disease Management) is a multicenter, observational, US-based study of the clinical course and disease management of PAH patients  $\geq 3$  months of age. All consecutive consenting patients diagnosed with World Health Organization (WHO) group 1 PAH according to specific hemodynamic criteria at participating institutions will be enrolled. Participating patients will be followed for a minimum of 5 years from the time of enrollment.<sup>26</sup> Adult patient registries include the Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA; NCT01347216 at <http://clinicaltrials.gov/>), which includes PH patients within 3 months of diagnosis; as such, COMPERA may serve as a template for a similar pediatric registry. The Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension (TOPP) registry is a global prospective study designed to provide information about demographics, diagnostic evaluation, treatment, and outcomes in pediatric PH.<sup>27</sup> The TOPP analysis defined important clinical features specific to pediatric PH patients ( $n = 362$ ).<sup>27</sup> Overall, 88% of PH patients had PAH (PH group 1, defined by the Venice classification 2003), which was idiopathic or familial PAH in 57% and associated with other disorders in 43%, of which 85% were associated with congenital heart disease; 12% had PH associated with respiratory disease/hypoxemia, with bronchopulmonary dysplasia found to be most frequent. A recent TOPP report found that most children with PH do not undergo the diagnostic workup currently used for adults, which probably emphasizes the inappropriateness of adult guidelines for children more than incomplete awareness of the current guidelines for adults with PH.<sup>28</sup>

*Childhood PVD networks?* To date, little attention has been given to the unique features of PPHVD:<sup>29,30</sup> a higher proportion of pediatric patients have PAH associated with congenital heart disease. In contrast to adults with Eisenmenger PAH, who have a better survival than those patients with idiopathic/heritable PAH (facing the highest risk of death), children with PAH associated with congenital heart disease have a 5-year mortality that is similar to that for idiopathic/heritable PAH (29% vs. 25%).<sup>26</sup>

Moreover, the gender ratio among children with PAH is nearly 1:1 (vs. 4:1 females in adult PAH), and it may be speculated that this is due to less influence of androgen/estrogen-type hormones in children versus adults. Furthermore, pathobiology, diagnosis, the number of approved PAH drugs, pharmacokinetics, adherence, and response to therapy is different in children versus adults with PHVD. Recently, the importance of age differences in the etiology, diagnosis, and treatment of PAH has been recognized by the American Heart Association (AHA) and the American Thoracic Society (ATS), and currently joined AHA/ATS guidelines for pediatric PH are in preparation. Moreover, a proposal for a classification of PPHVD specifically was published in 2011 and will undergo future revisions on the basis of feedback from healthcare providers and scientists (Box 1).<sup>29</sup> This PHVD classification (PVRI Panama, 2011) specifically designed for pediatric patients—although not quite internationally accepted—consists of 10 major PPHVD subgroups and emphasizes the unique features, such as the impact of lung development and heterogeneity of disease in neonates, infants, children, and adolescents. Such a more unified and specific classification may very well help PH experts to connect and enroll patients in clinical PH networks. The networks and according overview committees should also set standards for ethical conduct in these pediatric multicenter studies.

Because an interdisciplinary approach is needed for any specialized pediatric PH program, broad interdisciplinary expertise (pediatric cardiology, pulmonology, neonatology, and critical care) should be provided by the centers participating in such networks. A North American initiative from 2009 aims to bring PAH experts together to establish research and collaboration through the Pediatric Pulmonary Hypertension Network of North America, which currently includes six PH centers in the United States and two in Canada. Although this network has not enrolled any patients in prospective clinical PH studies yet, it is expected that it will incorporate additional PH centers and ultimately be successful in its efforts to start proof-of-concept studies, registries, and larger RCTs of novel drugs and drug combinations that are urgently needed for the efficient long-term treatment of progressive PVD.

## 2. Aim to achieve consensus on the major goals for pediatric PVD research and develop guidelines for diagnosis and treatment of pediatric PH

The above-mentioned AHA/ATS guidelines on pediatric PH will address the specifics of the disease in the pediatric populations as well as concomitant disorders, clinical evaluation (e.g., risk stratification, comparative effective-

ness), diagnosis and assessment of functional status, treatment, clinical follow-up, and future directions, including novel pharmacotherapies.<sup>14,31</sup> An according consensus document on adult PH was published by the AHA and the American College of Cardiology in 2009,<sup>32</sup> and European societies (ERS, ESC) published guidelines for adult PH in the same year.<sup>33</sup> It is important to distinguish between congenital heart disease/left-to-right shunts (1) with PVD (i.e., PPHVD) and (2) without PVD, because the latter PAH group benefits the most and primarily from shunt closure and subsequently often does not need long-term PAH pharmacotherapy. Moreover, single and biventricular circulations differ substantially in terms of hemodynamics and physiology, and they require distinct clinical definitions of PPHVD.

In 2010, the Division of Lung Diseases of the NHLBI, together with the Office of Rare Diseases Research (ORDR), held a workshop to identify priority areas and strategic goals to enhance and accelerate research that will result in improved understanding of the lung vasculature, translational research needs, and, ultimately, the care of patients with PVD (Strategic Plan for Lung Vascular Research: NHLBI-ORDR Workshop Report, 2010;<sup>25</sup> Box 2). In addition, a recent NHLBI workshop made suggestions on how to improve outcomes in PVD.<sup>34</sup>

## 3. Aim to enroll every PH patient with PVD/RVD in a properly designed clinical study

Whereas the patient database/registry should be managed centrally by one independent national or international expert institution, either academic or nonacademic, there are multiple capable trial-leading centers, each of which can run a separate diagnostic and/or therapeutic study that may or may not be a RCT (RCT registration, communication with data review board, etc.) and discuss trial-related issues with participating centers and potential collaborators. A trial-leading center may very well be a participating center in a different trial if the study design allows.

*What kind of studies should we enroll PAH patients into?* In the last two decades, improvements in the treatment of PAH patients have been made. However, none of published RCTs that lasted more than 16 weeks has shown a robust clinical benefit or a significant decrease in mortality with any of the current PAH treatments.<sup>19</sup> Hence, it is unlikely that future RCTs focusing on monotherapy or dual therapy with established (eventually chemically modified) PAH drugs (historically classified as vasodilators: endothelin 1 receptor antagonists, phosphodiesterase 5 inhibitors, and prostanoids) will substantially advance the field much further. The need for

**Box 1: Proposal for a classification of pediatric pulmonary hypertensive vascular disease (PPHVD; Pulmonary Vascular Research Institute, Panama Classification, 2011)**

1. Prenatal or developmental pulmonary hypertensive vascular disease
  - 1.1. Associated with maternal or placental abnormalities: chorioamnionitis, preeclampsia, and so on
  - 1.2. Associated with fetal pulmonary vascular maldevelopment: congenital alveolar dysplasia and so on
  - 1.3. Associated with cardiac fetal maldevelopment: premature closure of patent ductus arteriosus/Foramen ovale, obstructed total anomalous pulmonary venous return
2. Perinatal pulmonary vascular maladaptation (PPHN)
  - 2.1. Idiopathic PPHN
  - 2.2. Associated with or triggered by sepsis, meconium, congenital heart disease, diaphragmatic hernia trisomies, diazoxide, and so on
3. Pediatric cardiovascular disease
  - 3.1. Systemic to pulmonary shunts
  - 3.2. Postoperative pulmonary arterial hypertension after shunt closure, repair of dextro-transposition of the great arteries (d-TGA), tetralogy of Fallot (ToF), left heart obstruction, etc.
  - 3.3. Pulmonary vascular disease (PVD) following staged palliation for single-ventricle physiology
  - 3.4. PVD associated with congenital abnormalities of pulmonary arteries or veins
  - 3.5. Pulmonary venous hypertension
4. Bronchopulmonary dysplasia
  - 4.1. Associated with pulmonary vascular hypoplasia
  - 4.2. Associated with pulmonary vein stenosis
  - 4.3. Associated with left ventricular diastolic dysfunction
  - 4.4. Associated with systemic to pulmonary shunts (patent ductus arteriosus, atrial septal defect, ventricular septal defect, and aortopulmonary collaterals)
  - 4.5. Associated with significant hypercapnia and/or hypoxia
5. Isolated pediatric pulmonary hypertensive vascular disease
  - 5.1. Idiopathic
  - 5.2. Heritable
  - 5.3. Drugs and toxins
  - 5.4. Pulmonary venoocclusive disease and pulmonary capillary hemangiomatosis
6. Multifactorial PVD in congenital malformation syndromes
  - 6.1. With associated congenital heart disease
  - 6.2. Without associated congenital heart disease
7. Pediatric lung disease: cystic fibrosis, interstitial lung disease, sleep disordered breathing, and so on
8. Pediatric thromboembolic disease
9. Pediatric hypobaric hypoxic exposure
10. Pediatric PVD associated with other system disorders: portal hypertension; hematologic, oncologic, metabolic, and autoimmune disorders; and so on

This table shows an abbreviated schema; for a complete description, see Cerro et al.<sup>29</sup> Future modifications of this new PPHVD classification are expected. See also publications arising from the PH World Symposium in Nice, France (2013), under “Online Resources.”



**Box 2: Summary of recommendations to the National Heart, Lung, and Blood Institute on future pulmonary vascular research (from Erzurum et al.<sup>25</sup>)**

1. Advance basic scientific research in lung vascular biology utilizing emerging technologies
2. Advance and coordinate basic and clinical knowledge of the pulmonary circulation–right heart axis through novel research efforts utilizing multidisciplinary teams
3. Define interactions among lung vascular components, circulating elements, and systemic circulations by fostering novel collaborations
4. Encourage systems biology analysis to understand and define interactions between lung vascular genetics, epigenetics, metabolic pathways, and molecular signaling
5. Develop strategies using appropriate animal models to improve the understanding of the lung vasculature in health and in conditions that reflect human disease
6. Enhance translational research in lung vascular disease by comparing cellular and tissue abnormalities identified in animal models to those in human specimens
7. Improve lung vascular disease molecular and clinical phenotype coupling
8. Develop in vivo imaging techniques that assess structural changes in lung vasculature, metabolic shifts, functional cell responses, and right ventricular function
9. Develop research consortia that advance basic, translational, and clinical studies; allow for multicenter epidemiological study feasibility; and support training of junior investigators in lung vascular biology and disease

novel antiremodeling and reverse-remodeling pharmacotherapies with acceptable adverse effects is obvious.<sup>12,19,22</sup> New treatment modalities should be targeted to the genetic background and the most affected signaling pathways<sup>14,17</sup> in the individual patient (see below). Novel, innovative therapies need to be tested in clinical trial design adapted to both the complexity of the PAH (“PVD syndrome”) and the difficulties with sufficient patient recruitment and need to include proof-of-concept studies (see below, under no. 6) rather than only classic RCTs. As Stuart Rich pointed out, “I believe the era of the traditional RCT for PAH is probably over. PAH combines the challenges inherent to treating an orphan disease with a disease in which the knowledge of the molecular biology is complex and in advance of current medical therapies. (. . .) Academic investigators need to test new treatments of PAH based on animal models of PVD that better mimic human disease.”<sup>35</sup>

Recently, the Food and Drug Administration (FDA) launched the Critical Path Initiative to allow more adequate clinical trial design for diseases like PAH: adaptive design trials may facilitate more effective drug testing from the exploratory phase to the confirmatory phase. The Pulmonary Hypertension Academic Research Consortium (PHARC)<sup>36–38</sup> includes academics, regulatory (FDA) and research (NIH) institutions, and industry to plan landmark clinical and translational research activities in the field. The

PHARC is complemented by the Pulmonary Hypertension Global Clinical Trials Consortium.

**4. Carefully determine individual risk profiles and targeted therapies for PAH patients**

Genetic, circulatory, and environmental risk factors and disease modifiers should be carefully determined. Future goals are (1) individual risk assessment based on genetic screening and validated biomarkers, (2) clinical staging (e.g., functional status, RV anatomy and function by magnetic resonance imaging [MRI], and minimally invasive PA/lung biopsy when available), and (3) tailored therapy (within a centrally managed RCT): for example, peroxisome proliferator–activated receptor  $\gamma$  (PPAR $\gamma$ ) agonists may turn out to be particularly (but not exclusively) useful in PAH patients with bone morphogenetic protein receptor type 2 (BMPR2) dysfunction in the presence or absence of a known BMPR2 mutation.<sup>10,39,40</sup> In addition, metabolic modulators other than PPAR $\gamma$  agonists, such as the mitochondrial pyruvate dehydrogenase kinase inhibitor dichloroacetate,<sup>41–43</sup> might be very useful in the future treatment of PAH and cancer. Interestingly, the immunosuppressant drug tacrolimus (FK506) activates BMPR2, rescues endothelial dysfunction, and reverses PH in rodent models<sup>44</sup> and may open the door for “transplant medications” in pediatric PAH if confirmed in clinical studies. Finally, mesenchymal stem cell–related and endo-

thelial progenitor cell–related therapies have been proven to be efficient in preventing or reversing pulmonary vascular and parenchymal lung disease in rodents<sup>45-50</sup> and hold great promise for future autologous cell–related and heterologous cell–related therapies.

In pediatric medicine, new therapies are often adapted from adult RCT results. However, this was not the case in the trials for childhood leukemia. Nevertheless, it is intuitive that in children with PAH novel drugs should be administered only when sufficient safety and pharmacokinetic data in adults and children are available and the rationale for efficacy is evident. Consequently, it is most likely that for pediatric pilot trials drugs already approved for different indications (in children or at least adults) may be tested under rigorous safety monitoring. Such applicable drugs with the potential for efficacy in PAH may be approved by regulatory agencies. For example, the tyrosine kinase inhibitor imatinib has been used for rescue therapy in relapsed pediatric acute myeloid leukemia. Imatinib, more recently, has been studied in a phase 2<sup>51</sup> and phase 3 (IMPRES)<sup>52</sup> RCT in adult patients with advanced PAH receiving at least two PH medications: add-on therapy with the anticancer drug imatinib was shown to moderately improve 6-minute walk distance (6MWD; +32 m) and PVR in patients with advanced PAH, but serious adverse events (including subdural hematomas) and discontinuation of study drug were common.<sup>52</sup> These serious adverse events prevented FDA approval and make the addition of imatinib to standard PAH pharmacotherapy—at least in the near future—unlikely.

## 5. Choose tailored combination therapy early in progressive PAH

Choosing tailored combination therapy early in progressive PAH would require significant improvements in diagnosing PVD early and more comprehensively, for example, with MRI with or without angiography<sup>53-56</sup> and positron emission tomography.<sup>57</sup> Efficient North American, European, and international PH networks would be powerful tools to achieve this goal by validating new diagnostic and therapeutic approaches. The question of whether early combination pharmacotherapy should be applied to PAH patients with no or minor to moderate symptoms (WHO class 1 or 2) or only to those with more severe and progressive disease underlies an ongoing debate.

*PAH—hit it hard and early?* We simply do not know when the answer should be yes or no. The better we can determine the individual molecular signatures of PAH patients (see no. 4), the more likely it will be to limit the (costly) pharmacotherapy to one or two agents, thereby

reducing significant adverse effects. Supportive care and rehabilitation have been shown to have significant impact on the functional status (6MWD, maximum oxygen consumption on cardiopulmonary exercise testing) and subjective well-being of PAH patients<sup>58</sup> and therefore should accompany pharmacotherapy.

## 6. Define and explore new outcome measures for PAH trials

The 6MWD has been most commonly used measure in adult PAH trials even though it has shortcomings in predicting survival: individual fitness (conditioning) and other confounding factors, such as height, weight, and age, are not negligible. In addition, the 6-minute walk test is hardly useful in children with PAH: children and adolescents often walk >450 m in 6 minutes even in the setting of suprasystemic RV pressure and high brain natriuretic protein (BNP) levels while exercise test variables (e.g.,  $\dot{V}O_2\text{max}$ ) are often clearly abnormal. Both functional tests—that is, the 6MWD and spirometric exercise testing (treadmill, bicycle)—can often not be performed in patients <8 years old and in those with developmental delay (e.g., trisomy 21). The lack of reliable functional outcome measures in younger or handicapped children is a problem for clinical studies because the FDA requires a significant improvement in these functional (usually “primary”) outcomes in order to approve a drug for the indication “PAH (or PHVD) in childhood.” Moreover, in children with PH, assessment of functional class (such as WHO or New York Heart Association) was suggested to be pursued and newly defined by age group.<sup>30</sup> Hence, clinical end points beyond the 6MWD<sup>59</sup> need to be updated and validated in both adult<sup>60,61</sup> and pediatric<sup>62</sup> PAH trials. It should also be seriously considered whether primary outcomes other than functional improvement (e.g., 6MWD,  $\dot{V}O_2\text{max}$ , and change in functional class), such as PVR index, may be used as surrogate and primary outcomes in pediatric PAH trials.

Basic, translational, and clinical research efforts<sup>63</sup> should be directed to explore previously unknown PAH risk factors (environmental modifiers/metabolic dysfunction, such as insulin resistance and dyslipidemia,<sup>10</sup> and specific gene mutations), biochemical and cellular biomarkers (see no. 3), and other novel, more reliable, and convincingly validated (surrogate and combined) outcome measures. By doing so, genetic screening results may guide the search for new biomarkers and vice versa.

*Tiered strategy for agency approval of new PAH therapies.* Ghofrani et al.<sup>19</sup> proposed a tiered strategy for agency approval of new therapies for PH that gradually combines

anatomic (e.g., RV mass, volume, and ejection fraction), hemodynamic (e.g., mPAP, PVR, and RV function), and biochemical (e.g., BNP) biomarker end points with functional status (WHO class, 6MWD,  $\dot{V}O_2$ max, and beyond; see above), time to clinical worsening, and quality-of-life assessment. Such proof-of-concept studies can be conducted with a reasonable sample size (40–60 PAH patients) and designed as phase 1 (including drug metabolism/pharmacokinetics) or small phase 2/3 trials (see above, under no. 3). The results of these pilot studies may lead the way to patient registries and—in an ideal world—larger, multicenter RCTs for the efficient treatment of PAH that improves quality of life and survival.

### ONLINE RESOURCES

- Pulmonary Vascular Research Institute: <http://pvri.info>
- Pulmonary Hypertension Association: <http://www.phassociation.org>
- Pulmonary Vascular Disease NetWork: <http://www.chestnet.org/NetWorks/Pulmonary-Vascular-Disease-NetWork>
- Children's Oncology Group: <http://www.childrensoncologygroup.org>
- Society for Pediatric Oncology and Haematology (ALL-BFM 2000): <http://www.kinderkrebsinfo.de/gpoh>
- Medical Research Council and UKALL 2003: <http://www.mrc.ac.uk/Achievementsimpact/Storiesofimpact/Leukaemia/index.htm>, <http://www.ctsu.ox.ac.uk/search/StudyDetail.aspx?StudyID=1287>
- National Heart, Lung, and Blood Institute: <http://www.nhlbi.nih.gov>
- Pulmonary Hypertension Breakthrough Initiative, Cardiovascular Medical Research and Education Fund: <http://www.ipahresearch.org>
- National Institutes of Health Clinical Trials Database: <http://clinicaltrials.gov>
- Online supplement (open access): PH World Symposium, Nice 2013. Review articles at <http://content.onlinejacc.org/mobile/collection.aspx?categoryid=6325>

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