

## Future Directions: An Expert Panel Explores the Challenge of Halting Progression and Reversing the Pathology of PAH



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**Dr Gaine:** Let's start with you, Stuart. There has been a flurry of activity over the past few years with randomized trials and new drug approvals. Are we going to see a pause and a regrouping with the drugs we have? What is going to happen in the short to medium term with new drugs for pulmonary arterial hypertension?

**Dr Rich:** First of all, we are running out of patients. So we are limited in our ability to place them in clinical trials by the absence of a patient base. Currently the general categories of drugs that have been developed are the endothelin receptor blockers, the PD5 inhibitors, and the prostacyclins. I think from this point on we will see new drugs within these categories. You are going to probably see similar efficacy within the class. But we will start seeing that some classes of drugs have superior efficacy over others. I have my own thought about which is the most efficacious and which is the least, and I don't think we need any more of these "vasodilator" types of drugs. Hopefully a newer generation of treatments will come from an attack on the appropriate molecular pathways. We now understand what triggers the disease, what pathways are involved, and it may be time for pharmacogenomic therapy or really trying to do disease reversal as opposed to disease palliation.

**Dr Morrell:** I agree that we will see more drugs of the same class as the ET receptor antagonists and PD5 inhibitors, and of course the combination of these

agents. However, I would continue to encourage active clinical research with vasodilators. We know that many of the vasodilator pathways also affect the structure of the vessel wall, probably by influencing growth and apoptosis. Some of these pathways exert more profound influences than others. Take for example the success of ACE inhibitors in the treatment of systemic hypertension and left ventricular hypertrophy. In the same way it is likely that some of these pathways exert a more profound effect than others in the pulmonary circulation. For example, we have not yet begun to reap the clinical benefits of the basic research into the serotonin pathway. On the vasodilator side, agents such as vasoactive intestinal peptide and adrenomedullin may prove even more effective than prostacyclin. We just don't know yet.

**Dr Gaine:** Stuart, you started by saying that we are running out of patients. Will you explain that?

**Dr Rich:** Well, it is a phenomenon related to the fact that the first approved therapy, which is intravenous prostacyclin, is lifesaving. We are at a point where the feeling is that it is unethical to have any patient untreated. So to do placebo-controlled trials is going to be quite difficult unless you choose the most minimally symptomatic patients. But remember when you do treat diseases, the most minimally symptomatic patients will show the least. It will take a large number of patients and will be difficult to do. For the more advanced cases there are existing therapies that improve quality of life, exercise tolerance, and survival. Most people feel it would be unethical to do a randomized trial against placebo in those patients. So now you are talking about either head-to-head superiority trials or noninferiority trials, and those take large numbers of patients, which don't exist in the pulmonary hypertension arena. So I think it is going to be very difficult to introduce a whole new drug into this arena, given the limited patient base.

**Dr Voelkel:** I was initially also a little confused when Stuart said we were running out of patients, and I think he saves himself in the latter part of his argument. My take is that we are looking, and I agree with him totally, at new treatment paradigms, categorically new treatment paradigms. Enough of the vasodila-

tors, we have had that experience. We probably will never get a better vasodilator than prostacyclin. So the reality is that we are dealing with patients who are being helped initially. They are stabilized, they are improved, and then we run out of gas, they run out of gas. My take on this is that we design studies for patients currently receiving established maximal therapy with the goal of saving them, rather than at the end of the day still transplanting them. Stuart, do you agree?

**Dr Rich:** Totally, Norbert.

**Dr Morrell:** Of course it would be foolish to focus all efforts on so-called vasodilators, but I believe there is still some mileage left in this approach. However, I do agree that the overall benefits will be incremental rather than revolutionary. We need to turn our attention to taking advantage of the major new insights into the molecular pathogenesis of PAH that have emerged over the past few years.

**Dr Voelkel:** I will work with anybody who will find an interesting target. There are plenty of those patients around because they are all registered and on the Actelion distributorship, patients on prostacyclin year four. Whenever you look at them hemodynamically, or do follow-up echocardiography, their systolic pulmonary artery pressure is 80 mm Hg, and we don't know where they're going. Are they going to crash in two years? I don't think we have anything else to offer. With the best of our abilities, we are keeping them in a stable or pseudostable form. But I think there are lots of these patients around.

**Dr Rich:** No doubt. We have been focusing until now on trying to slow disease progression and our data show that patients aren't dying as fast, but they are dying. The new challenge is to try to halt progression and induce regression. And we'll probably start with that group you've identified, patients receiving maximal therapy who are still very sick,

**Dr Gaine:** You've brought up twice now the notion of disease regression therapies and I wonder if we could elaborate on that. Diseases of the lung like emphysema or pulmonary fibrosis result in parenchymal destruction with no reasonable chance of reversing that process. But the pathology in pulmonary arterial hypertension reveals proliferation of cells rather than destruction or loss of tissue, leaving open the hope that we may be able to reverse the pathological changes in the future. What thoughts do you all have on the way that is going to evolve?

**Dr Voelkel:** Well, I can tell you what my fantasies are. The comparison with interstitial fibrosis or emphysema is, thankfully, problematic in a good sense, because I do not believe you have the same degree of global destruction. I say this because most of the vascular lesions are in strategic locations in the lung circulation. This is where the work with our three-dimensional reconstruction comes in. A published report (Cool CD, et al. *Am J Pathol.* 1999;155:411-419) indicated that if you follow down the vascular tree, eventually you come to a blockage, but it's not

If we believe there are switches that turn the disease on, there should be the ability to turn the disease off, at least in theory. I think it is going to take understanding the molecular biology of what goes on. Whether it comes down to inducing apoptosis or to blocking a transporter or to inducing a growth factor or a growth inhibitor, I don't think we know yet. But I think we will find our way to saying that if we affect a certain fundamental biological process, the disease will shut down.

like an embolus that's about 15 mm long, it's still a microscopically small lesion. If the focus is on these abnormal cells, and if we are smart enough to figure out how we can remove the abnormal cells, we can be ultimately successful. You can calculate how many of these vessels have to be occluded in a human lung before the mean pulmonary artery pressure goes up to, let's say 50 mm Hg. People will tell you that you probably have to have 95% or more of these strategically localized arterial lesions occluded before the mean pressure gets so high. I think to have a goal to make all these vessels squeaky clean again would be unrealistic. But if we can perhaps open up 20% or 25% of these vessels, you can make the calculations, the pulmonary artery pressure would have to fall, and fall substantially. It would never be entirely normal, but the patients would be out of the danger zone and I don't think they would ever have to go into right heart failure and die. That's my fantasy in a nutshell. I think it's realistic to say that if we can open up 20% or so of these vessels, it would have very big hemodynamic consequences and lead to a large improvement.

**Dr Gaine:** Nevertheless, is it not reasonable to think it is a fantasy that can become a therapeutic reality? Do people believe there are switches we can flick to tell the vasculature to reverse the proliferation?

**Dr Rich:** Probably. I am always amazed at the body's ability to correct disease processes, more than we ever thought. The late Professor CA Wagenvoort wrote a paper in the 1980s subtitled "The point of no return" (*Minn Med.* 1985;68:45-48). The pathologist had a viewpoint that if certain lesions were present, histologically, the disease was irreversible. But I think that has been proved wrong many times with other organs. So I think Norbert's fantasy is not really fantasy. There are some changes that are likely never to return to normal. But it is remarkable when you look at postmortem lungs how heterogeneously the vessels are affected, and he is right that you may not need to reverse 100%. You may just need to reverse 10% or 15% or 20%. The goal need not be normal, but the goal should be stable. If patients are going to be able to go to work and have a reasonable quality of life, with some limitations, I think that is total victory.

**Dr Voelkel:** I totally agree with you. That's why we can't really make the analogy with interstitial fibrosis or with emphysema. When you talk about lung volume, I mean just lung parenchyma, you have, pound for pound, a much greater and more ubiquitous destruction in both of these diseases. When you look at very bad emphysema, patients who have a diffusion capacity of 30% of predicted, all they basically have left on the right side of the lung are two alveoli and on the left side maybe 3.5. That is not so in the pulmonary hypertensive disorders because, luckily, the rest of the parenchyma is OK. The vascular obliterations, the sites where there is no flow—and if you look at it longitudinally, as you walk down the vascular tree—are still very small. If this were all cast with glue and you had many mil-

limeters of these vessels that were occluded, I would not be as hopeful as I am right now. When you do a three-dimensional reconstruction of the vasculature, you appreciate how localized that process is.

**Dr Morrell:** The same is true in some animal models of this disease. Although the vascular lesions are not the same as in PAH, such studies have at least demonstrated the potential for advanced obliterative vascular lesions to regress. This was elegantly shown by Marlene Rabinovitch's group a couple of years ago, when they showed that inhibition of vascular elastase could have a dramatic effect on established vascular remodeling.

**Dr Gaine:** Would you speculate on how you might achieve that fantasy, meaning, would we be using drugs that might induce apoptosis in the cells in that area? Would we be using gene-based therapies?

**Dr Rich:** You've asked whether people think there are really switches. I think the answer is yes. If we believe there are switches that turn the disease on, there should be the ability to turn the disease off, at least in theory. I think it is going to take understanding the molecular biology of what goes on. Whether it comes down to inducing apoptosis or to blocking a transporter or to inducing a growth factor or a growth inhibitor, I don't think we know yet. But I think we will find our way to saying that if we affect a certain fundamental biological process, the disease will shut down.

**Dr Morrell:** The two components of our approach to vascular obliteration as described by Norbert should be to prevent further obliterative lesions and to induce regression of those already established. It may be that some so-called vasodilator drugs will have some effect on the former, but we will need a whole new approach to achieve the latter. The induction of apoptosis in the obliterating lesions is an attractive approach. We already know a lot about the mechanisms regulating apoptosis in vascular cells, but the problem will be in directing this process to the offending cells without causing the whole lung to fall apart. Closer study of the cells that make up these lesions may reveal pathways that are restricted to these cells and could allow targeting of therapy. For example, they may overexpress survival factors or receptors, which are lacking on the neighboring normal cells. Actually therapy in PAH is perhaps one example where a gene therapy approach would not suffer from the same limitations as in some other conditions. If the object of therapy were to reduce the number of obliterative lesions, then prolonged expression of genes delivered to the pulmonary circulation would not be essential. Repeated short-duration exposure to proapoptotic genes may be sufficient to cause lesion regression and allow existing therapies to prevent further lesion formation. The problem with gene therapy for some other lung diseases, such as cystic fibrosis, is that prolonged expression of the therapeutic gene is needed.

**Dr Voelkel:** In vascular biology we talk about an angiogenic switch. Stuart is correct. If we can find out what the particular switch is in our disease, we would be very much helped.

Another thing I can say is that we have worked the last three years with an animal model of severe pulmonary hypertension where the mean pulmonary artery pressure is somewhere between 50 and 65 mm Hg. That is a lethal form of pulmonary hypertension (Taraseviciene L, et al. *FASEB J.* 2001;15:427-438), and we were able to reopen some of the previously obliterated vessels by inducing apoptosis. So Stuart is correct again. I think there are two points of the attack: one is to identify the angiogenic switch and the other is to make peace with the idea that the cells are there, that they are not normal muscle and endothelial cells, and that we need to find out how to remove them, probably with the induction of apoptosis.

**Dr Gaine:** Two important questions arise in terms of future directions and treatment. One is the issue of placebo-controlled trials. First, are we finished with placebo-controlled trials, or do we have a small window left? Second, given the evidence recently from Olivier Sitbon and the French group that the number of people who are going to benefit from calcium channel blocker therapy is significantly less than 10%, are we going to see the day soon where the vasodilator trial is considered irrelevant and not included in the therapeutic algorithm?

**Dr Rich:** No, it is not impossible to do it, it is just going to be a matter of trial design. If your end point is measured over a very short interval, let's say two weeks, you could probably justify putting most patients in a trial for two weeks and randomize to placebo. If your end point is a year, you have a whole different ethical issue in terms of risk. Sean, it also depends on what the therapies are designed to do and what kind of end point you choose, but clearly we've shown that we can make people feel better, walk farther, and live longer. And ethics demand that you inform patients that participating in a trial and being randomized to placebo will jeopardize them with respect to such benefits. The other option is to compare treatments, but that would mean superiority or noninferiority trials requiring many patients. I don't think the pharmaceutical industry has enough interest in this disease to invest what it would take to do that.

**Dr Voelkel:** I think everybody agrees that we all do our job with trying not to miss things that are particular to this and not to the other patient. That's why we have to take all patients on a very individual basis. But I am a little concerned about a practice I'm beginning to see. It has to do with people who are not very experienced with pulmonary hypertension patients giving them endothelin receptor blockers. We used to have relatively few patients come to us who were supposedly getting "good treatment." Now we are seeing patients coming to us after two months or so of treatment with an endothelin receptor blocker, and they are not doing well. I don't know whether this is going to spread around the country, with more practitioners saying, because of effective advertisement, well, there's a drug that's an oral agent, it's easy to use, we only have to check liver function tests, and we can do that. Stuart, what do you think?

**Dr Rich:** Well, you know, Norbert, this was expected to happen. The practice of medicine in this country does not require you to have certification to prescribe a certain medication. It is so

interesting how this disease therapy has evolved, because the best therapy that we have is the first one that we've ever tested, and that's epoprostenol. Our mission is to try to avoid using it. Now that we have bosentan, physicians ask, "Do I need to refer this patient? What's the downside if we treat first? Why can't I treat first and diagnose later?" There is nothing we can do to prevent that, so all I can say is that it is almost a predicted consequence of the approval of the oral agent that physicians with less expertise are going to use it. It was kind of a honeymoon period, if you will, when the therapy was so complex that it almost mandated that only a specialist could use it. But the honeymoon is over.

**A major recent breakthrough is the identification of mutations in the bone morphogenetic protein type II receptor (BMPR2), which underlie at least 55% of cases of familial primary pulmonary hypertension. Having a mutation in BMPR2 is the biggest risk factor for PAH yet identified, by orders of magnitude.**

**Dr Morrell:** It's the same in the UK, with increasing use of oral drugs outside the specialist centers, though this is being resisted. We all know that patients with PAH are a complex and heterogeneous group. This is often not appreciated outside the centers and the problem is that patients may be deprived of timely intervention with prostanoids, atrial septostomy, or transplantation

**Dr Voelkel:** I think a consequence of what you developed is that we have a bit of a responsibility to tell practicing physicians that unfortunately it's not going to be so easy, that you can't just pop the bosentan and hope for the best.

**Dr Rich:** I lived through the same thing with calcium blockers. We published a paper showing there is a subset of patients who have a really remarkable response. And what happened is that calcium blockers became an automatic treatment for any person with an elevated pulmonary pressure for any reason. How many of those patients never made it to see us because their referral was inappropriately delayed because of the calcium blocker? How many were worsened and put into right heart failure because of calcium blockers? This has become a two-edged sword. I think you are going to see the same thing with the endothelin receptor blockers, and potentially with any oral agent, that is, physicians who use it and don't know how to monitor.

**Dr Voelkel:** All I am saying, Stuart, is that what you have already started, this detective work, is something we need to continue to do. It is our responsibility to get that information out. I wish you had published that calcium experience paper.

**Dr Gaine:** Now is a good time to consider publication of those data because they teach us how starting with a particular therapy for defined indications can quickly get lost when translated to the wider physician pool.

**Dr Voelkel:** The categorical problem remains, Sean, that from our point of view, if you want the dissenter's view, we continue to face the problem of what we would call delay of maximal treatment. The diagnosis is delayed at the start because of asthma as the principal first misdiagnosis. Then the diagnosis is made because somebody finally orders an echocardiogram. We now will have an additional phase where some of the patients

will become severely ill because of treatment that, perhaps, is not optimal.

**Dr Gaine:** In the time remaining we will explore basic science and I will start with you, Norbert. You and your colleagues had a fascinating paper recently concerning risk factors for pulmonary hypertension (Cool CD, et al. *N Engl J Med.* 2003 Sep 18;349:1107-1109). Are there going to be more viruses?

**Dr Voelkel:** Retrospectively it is always easier to make statements, and hindsight is always 20/20. From where we stand now we could have learned a little more about some of these things in primary

pulmonary hypertension if we had thought through the human immunodeficiency virus story. What it means for me now is that what HIV infection and herpes virus infection have in common is some degree of immune insufficiency. This is something to hold on to. If you have, let's say a 60% rate (and this has to be confirmed by other groups) of infection with herpes virus in patients with primary pulmonary hypertension, then many, many questions follow. One that you raised concerns the other ones, where we have not identified the HHV-8 strain, those caused by other virus infections. Indeed, we take the position that we have to search further for other viral agents and we have ideas about that. The second one is, what is it about the immune system? Stuart is one of the early people who published that 30% of patients with PPH, that we honestly call PPH, have a positive LANA. So, that spectrum of the immune response, one moving toward an autoimmune process, and perhaps as importantly, showing us a face of immune insufficiency, is getting very important.

Take the data from the French group, from Marc Humbert, who published data about elevated plasma cytokine levels. Well, that goes with a viral infection pattern. Work has to go on in this direction for it to have consequences for diagnosis because we may have blood tests of some kind that will help us identify the virally infected patients.

**Dr Morrell:** The viral hypothesis is an attractive one, though to be a devil's advocate, it's one that's raised its head in many other chronic inflammatory and autoimmune diseases over the years. However, the lungs are uniquely exposed to airborne viruses and the exclusive susceptibility of the lung circulation to the obliterative process in PAH makes viral exposure a compelling hypothesis in this setting. The observations on HHV-8 are an intriguing breakthrough that urgently need confirmation by other groups and studies of potential mechanisms. Of course, the other major recent breakthrough is the identification of mutations in the bone morphogenetic protein type II receptor (BMPR2), which underlie at least 55% of cases of familial primary pulmonary hypertension. Having a mutation in BMPR2 is the biggest risk factor for PAH yet identified, by orders of magnitude. This vital piece of genetic evidence provides a solid basis from which to begin to unpick the molecular pathogenesis of PAH. Clearly other factors are also involved, which may include viral infection. Several groups are working on precisely how these mutations contribute to the develop-



ment of obliterative lesions in PAH. Personally, I believe this approach will yield novel therapeutic options within a relatively short period.

**Dr Gaine:** Stuart, what are your thoughts on risk factors and future directions?

**Dr Rich:** Well, Norbert is really the molecular biologist and I am more the epidemiologist, so let me wear that hat for a second. PPH has so many variations. Probably a number of different molecular pathways can be involved, and you may need a certain critical number to come down with it clinically. That may be why some patients are vasoreactive and some are not, and some have a good response to this drug and some do not. The work Norbert has done, and the work that supports this, is absolutely on the money. There probably are some patients who through some abnormal immune modulation have further disease expression, but there are probably others who don't, who have different things, such as patients in the fen-phen group, who may have had the drug turn on a certain switch. So I think a generation from now they'll look back and see that we were at an embryonic stage here, that PPH is really the final consequence of abnormalities in several pathways that lead to it. Looking at this from a broader perspective leads me to believe all of this work is going to be important, but there is not going to be a single answer to this disease, there are going to be a lot of answers.

**Dr Voelkel:** The basic epidemiology, Stuart, will remain, that for any identified or identifiable risk factor, the denominator is always very, very large. So if 17 million Americans took fen-phen and you end up with a few thousand (even if we don't know all of the patients who will still develop the disease), the denominator of those who were potentially at risk is huge. The same of course has been true for the AIDS association, and I assume it will be exactly the same for the KS virus association. If you look at the blood donor pool in America, I think the numbers are about 3% or so of US blood donors, you can show there is evidence for herpes virus 8 infection. If you go closer to the Mediterranean, it goes up to about 20%. But that doesn't mean the incidence of primary pulmonary hypertension necessarily goes up with it. I don't think we have the understanding that just because you move closer to the Mediterranean Sea the numbers of patients with primary pulmonary hypertension are much higher. I don't think they are.

**Dr Rich:** No. I think we agree there, Norbert. What I am getting at is that all of these new risk factors and the roles they may play are starting to be uncovered and described, that we shouldn't think there is going to be a single answer here, and that it is going to require several defects within the whole vascular control milieu, if you will, in order to contract this disease.

**Dr Voelkel:** I agree. You have to have some kind of a basic genetic disposition, which we don't understand at this moment. And there are multiple trigger factors that, alone or in combination, in a susceptible person trigger the disease. But my take is that the common denominator at the end is the angioproliferative process, and that there are many ways you can get there.

**Dr Rich:** It is fascinating to go back to old news of the histology, from all of those papers published decades ago. A lot of people who died with PPH had just medial hypertrophy, but others had advanced concentric laminar intimal fibrosis and plexiform lesions everywhere. I can't believe the molecular process is the same in both instances.

**Dr Voelkel:** But Stuart, I think a lot of the old literature is contaminated by not shining the correct searchlight on the tissue. People did not stain for angioproliferative processes. Most of the old pathologists looked to find a plexiform lesion, and if you don't look in multiple sections, in particular in the subpleural regions, you sometimes miss them. So I would not be too confident in some of the old literature. I think we are getting better, and we are looking harder, and we are finding more.

**Dr Gaine:** Are there things maybe we haven't touched on that you think we should?

**Dr Rich:** Yes. This is a disease of right heart failure. One thing that's intrigued me and that I don't think we have focused enough on, is the fact that there are patients, congenital heart disease patients, who have severe pulmonary hypertension and minimal limitation with respect to their physical activities because of the tremendous ability of their right ventricles to hypertrophy and adapt to the pressure load. I attribute that to the expression of fetal genes and it is apparent if the insult occurs when you are a baby as opposed to when you are an adult. A lot could also be achieved by looking not just at the pulmonary vasculature, but at the ventricle itself and asking how we can program these hearts to better adapt to the pressure load. We may never be able to relieve the pressure load, but if we can get the ventricle to adapt to the pressure load, the patients might live almost normally. So an area of potential gain that hasn't really been touched on is genetic control over myocardial performance and trying to get the ventricle to better adapt.

**Dr Gaine:** If only we could teach right heart myocytes to believe they are actually left heart myocytes, or switch on the left heart differentiating genes, then the heart would last a lot longer despite the pressures.

**Dr Rich:** In utero they are the same. Some genes are turned off when the baby is born. We need to switch those genes back on.

**Dr Voelkel:** No question about that. People die of right heart failure. That's very important, and perhaps a future conference should have a very sharp focus on that particular issue of the right ventricle.

**Dr Gaine:** Cardiologists, when looking at coronary artery heart disease and left heart failure, are years ahead in terms of drugs and procedures compared with their colleagues in the field of right heart failure and pulmonary vascular disease. In this regard, are there any drugs or tools that are beneficial in left heart disease that might translate into future directions in the treatment of the right heart? I'm thinking in terms of surgical procedures that might help the right heart, mechanical assist devices, or electrical pacing, etc.

**Dr Voelkel:** I wouldn't think of electrical mechanical devices. I think the strategies will, at the end of the day, have to be molecular strategies, where you do what Stuart suggested. You have to basically generate an Eisenmenger right ventricle and that

would be the concept to follow. If we could do that with molecular tools and get good quality, strong, robust right ventricular muscle, we would be saving a lot of people.

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## Role of BMPR2 Mutations in Pathogenesis of PPH

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