# Conference Impressions and Applications

Guest Editor and Conference Scientific Sessions Chair Vinicio de Jesus Perez assembled a group of attendees to discuss their experiences at PHA's International Conference and Scientific Sessions in Orlando in June 2018. Participating in the conversation were Zhiyu Dai, PhD, Research Assistant Professor in the Department of Pediatrics at Northwestern University Feinberg School of Medicine, Chicago; Elena Goncharova, PhD, Associate Professor of Medicine and Bioengineering and head of PH Basic Research, Center for Pulmonary Vascular Biology and Medicine, Pulmonary, Allergy & Critical Care Division, University of Pittsburgh Department of Medicine; Kara Goss, MD, Assistant Professor, Division of Allergy, Pulmonary and Critical Care, University of Wisconsin, Madison; and Tim Lahm, MD, Associate Professor, Department of Medicine, Indiana University School of Medicine. Adding to the conversation was Jair Tonorio, PhD, Research Associate, Hospital Universitario La Paz, Madrid, Spain.

**Dr de Jesus Perez:** Elena, please start us off with your experience with the conference.

**Dr Goncharova:** This is my first conference of this sort. I've been overwhelmed by the fantastic organization and by the chance to see the PAH patients. And, of course, by the very strong selection of speakers for the scientific sessions.

**Dr de Jesus Perez:** How about you, Tim? You are also a veteran of the Conference.

**Dr Lahm:** Right. So, I come with a little bit of a different perspective. I think this was my sixth or seventh Conference, and I was just amazed by how large the Conference has become. It seems to be getting bigger every time it's held. I remember a few years ago, it was in the same location and it was much smaller then. So just the sheer growth and energy of the Conference is really what amazed me. It's just terrific to see all this energy and growth, both on the provider side but particularly on the side of the patients and their caregivers. It's just so much enthusiasm and positive energy. I thought this was really terrific.

**Dr de Jesus Perez:** How about for you, Kara?

**Dr Goss:** I think what amazed me again, yet again—so this is my third or fourth Conference—was the enthusiasm of the patients, in particular. You know, that's really why we're all there, why this Conference happens, is because we are providers who treat patients; but at the end of the day this is all about making life better for patients. And they show up in droves! They have pumps and oxygen and may have a motorized scooter or something else. It's not easy for them to come to Conference, and yet they love coming to Conference. It's one of their highlights of the year. And so their energy, I think, is really infectious to everybody. I actually led a session for the adolescent group on Sunday morning. It was scheduled for 8:00 Sunday morning. And I thought there is no way you're going to get a bunch of teenagers…

**Dr de Jesus Perez:** Yeah (laughter).

**Dr Goss:** … to do an adolescent discussion breakout session Sunday at 8:00am. I'm thinking, they will all be asleep, you know, at worst, or maybe off having breakfast. And yet, we had a great turnout. I think that really speaks to how invested the patients are. And they're the reason that we have these Conferences and keep pushing to move the field forward and have this sort of multidisciplinary interaction, to keep moving forward.

**Dr de Jesus Perez:** Great. How about you, Zhiyu? What were your impressions?

**Dr Dai:** It was a good experience! I got the chance to present my work and interact with senior PIs, like Vinicio. His advice is very important to my career development. Most importantly, I had the chance to interact with the patients, because I'm a bench worker and I don't have a chance to interact with patients. I had the chance to meet with the founder of the Pulmonary Hypertension Association in China, a former patient that has received 2 lung transplants and is doing great right now. She started an organization to help the patients in China, where the population is 3-fold compared to the US. I think those kinds of experiences will encourage me to do the research and hope to develop some kind of treatment.

**Dr Tenorio:** I would like to add my point of view of the Conference. It was my first time at the PHA Conference. In my case, I cannot give a stronger relationship between scientist, caregivers, patients, and industry than my own experience. I was invited by the Spanish Foundation against PAH, so I attended with the president of the foundation. He is trying to translate the knowledge and advances of PAH diagnosis and treatment to Spain and at the same time be "on the peak of the wave" with the advances in the treatment of PAH. He is the lead voice of the patient abroad and he transmitted to me the courage and the feelings of the patients and parents of patients, which is my motivation to continue working for a better understanding of this disease. I think it is mandatory that we all give voice and share the different aspects from different points of view. This forum was a perfect way to do that.

**Dr de Jesus Perez:** That was great, guys. So now, I want to dig a little bit deeper into what the Conference meant for



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each of you professionally. Kara, you were running the research room this year at the Conference. The research room is one of the most important aspects of this meeting, since it is a bridge between patients and physicians. It allows us not only to connect with patients to obtain samples and data that will be critical for research, but also to connect with the patients at a deeper level. We want to show the patients how deeply involved we are in trying to understand and figure out ways to cure the disease. What was your experience, Kara?

**Dr Goss:** I think we had an outstanding representation in the research room this year. I believe we had 10 investigator teams, as well as more than 200 research participants. And the amazing thing there is that our research participants are patients, family members, physicians, people not related who just happened to be at Conference. Really, we take all comers because there are so many different types of research going on in the research room, that we have literally something for everyone. We had several study teams drawing blood to be able to take samples back to their labs. And for some of those labs, it's one of their primary ways to interact with patients, to be able to see patients and talk with them and learn a little bit about their histories before they take their samples back to their labs. For other investigative teams, they were doing more qualitative research, with surveys trying to understand what things about life and lifestyle are most important to our patients. For example, exercise, intimacy issues, or general quality of life sort of questionnaires. And then, there was one group asking about how we can improve the delivery of health care, using specific technologies and applications designed for physicians and providers. So really, there were all sorts of different things happening in the research room. It's a wonderful way to bring those sorts of ideas and investigators together, so we can tackle the full breadth and scope of the problem that pulmonary hypertension poses. I know for me, leading the research room team this year has been a wonderful experience. The Pulmonary Hypertension Association has done a fantastic job with much of the preparation. They actually made my job fairly easy for bringing all of this together. And it's been a great way for me to get to know other providers and researchers within the pulmonary hypertension community, as well.

**Dr de Jesus Perez:** That is great to hear. Speaking of the impact on the patient community, I think the scientific sessions this year had a very interesting topic that related to both physicians and patients and their expectations regarding the future of health care for pulmonary hypertension. We talked about precision medicine and the many different ways it can help us. But we also were able to discuss those areas that may be more problematic or that could potentially affect how these technological advances become part of the standard of care. I just want to spend some time discussing this with all of you. Tim, you were moderating the session on 'Omics and wearables. What was the take-home message from that panel?

**Dr Lahm:** First of all, thanks to you for organizing this, Vinicio. You really put together a terrific program. I was really amazed about it. As you were saying, I had the privilege of leading a session on 'Omics and wearables. Interestingly, from a thematic standpoint, this is a session that could have been held at any disease symposium. If you look at this topic as a whole, there's not much specific to PH; this could have been held at a diabetes symposium, right? Or at a systemic hypertension symposium. I thought this was a really nice example of how the field of PH has grown. A few years ago at this meeting we had discussions about new diagnostics or new treatment approaches and new drugs. It's amazing to see how the field has grown—now we talk about wearables for pulmonary hypertension and big data approaches for pulmonary hypertension. It's just an indicator of the tremendous growth in the field. I have to say, I really enjoyed the talk by Mike Snyder on wearables. I'm not even sure if he used the term "pulmonary hypertension" once. He talked a lot about diabetes; he talked about Lyme disease. And by doing this, he provided terrific examples of how we can learn from other diseases and from the general use of technology. That was really interesting to hear. So I think PH has really arrived in the field of modern medicine. We're not just talking about endothelium, prostacyclin, and nitric oxide anymore. We talk about 'Omics; we talk about wearables; we talk about implanted devices. It's really outstanding to see that. I think the audience felt like that as well. We started our session at 8:15AM on a Friday. And even at 4:15 on a Friday afternoon, the room was packed—and not just with physicians or health care providers. There were a lot of patients and caregivers as well. So I think it really shows that there's a lot of appetite for learning about these wearables and implantable devices and big data approaches in PH.

**Dr Tenorio:** I completely agree with Tim. Nowadays, 'Omics and precision medicine are 2 new ways to not only do research but also to treat patients specifically according to their specific needs. A great example of how 'Omics is changing PH is the PVDOMICS consortium project, presented by Dr Hemnes. It's now clear that patients with PH can have different molecular profiles that have to be specifically managed, and could be totally different, even in 2 patients with the same etiology of the disease. This means that a new standardized nomenclature based on the molecular profiling will assist in accurately classifying patients. These presentations were very impressive and highlight the importance of these projects to finally give a better response of what patients demand of us.

**Dr de Jesus Perez:** So, Elena, you also were leading one of the panels, the one on basic science and clinical trials. And there was quite a lot of discussion generated by the presentations given by Dr Marlene Rabinovitch, Steve Kawut, and Harm Bogaard. Can you summarize for us what were the highlights of the discussion?

**Dr Goncharova:** Gladly. First, I wanted to thank you for the opportunity to moderate such a great session. It's an

honor to moderate a session with such fantastic speakers. It was a very nice balance and flow of basic and clinical-oriented presentations in which basic science talk led to translational and after that clinical studies. Marlene Rabinovitch delivered a fantastic talk on overseeing new basic science approaches. Importantly, in the final part of her talk she presented a new study on the use of patient-derived iPSCs for potential diagnostic purposes. Steve Kawut had been talking about clinical trials and I believe that most important for us is how both his and Marlene's talks highlighted the personalized medicine approach as our future direction. We consider every patient unique, we want to do the best science and find the best clinical solution for each individual patient.

**Dr de Jesus Perez:** Zhiyu, what were you the most excited about, of all the things that were discussed that day at the scientific session? What was the one thing that really got you excited about going back to work?

**Dr Dai:** One of those talks was presented by Dr. Harm Bogaard on the right ventricle, a topic that has been difficult for me to quite figure out. However, this session totally opened my mind to the possibilities in the field. In my research, I found that in our Egln1 knock out mice there is a lot of endothelial cell proliferation in the right ventricle. However, despite evidence for abundant vasculature, these mice still have right heart failure. From the talk by Dr Bogaard, it is apparent that because the right ventricular hypertrophy requires a higher supply of oxygen or more nutrition, that will induce endothelial cell proliferation. Thus, I speculate that despite a higher rate of endothelial proliferation, this might not be enough to supply adequate oxygen or nutrition to the right ventricle. Other talks by leaders in the field of PH research, such as the talk presented by Dr Marlene Rabinovitch, inspired me to take newer approaches in my future studies.

**Dr de Jesus Perez:** I want to open it up to everyone right now. I think to me, one of the most intriguing—and maybe provocative—sessions was the one that involved discussion on pathways to future PH therapies. We were lucky to have Dr Norman Stockbridge from the FDA, tell us about what the FDA wants for new PH therapy development and approval. I thought this was probably one of the most intriguing and probably open-ended sessions we actually had. I want to hear from all of you guys, scientists and clinicians alike. What did you think at the end? Did you feel hopeful? Did you feel hindered in terms of what is expected from us in order to get new therapies out there in the patient community?

**Dr Lahm:** Yeah, Vinicio, I have to say I feel hopeful. I think the PH field has done a nice job in constantly evaluating the way we perform our trials. I think a lot of this has to do with ongoing conversations with the FDA. It's not always easy to critically acclaim what you are doing or what you have done. Sometimes, you have to admit that you did things wrong or that you did things not in a way you wanted to do them originally. But I think we have learned a lot by doing that. For example, look at the initial trials that were performed: we looked at 6-minute walk distance and 12- or 16-week outcomes. And now our trials have gotten so much more sophisticated. They are harder to do; I think we all acknowledge that. But I think we also appreciate the benefits of performing more sophisticated studies, and we all know it's worth it, since we think this directly translates into better patient outcomes. I think this also helps to get everybody on board: the scientific community, the industry, the FDA. I know a lot of companies didn't want to do the trials the way we are doing them now. But I think through ongoing conversations, like the ones we had at the meeting, everybody understands the importance of doing trials the right way, even if it's hard. I think that the same holds true for basic scientists. The right thing to do often takes much more work and requires more money. It takes more effort; it takes more people. But at the end of the day, it's worth it. So I think it's important to have these conversations, even though they're not always easy.

**Dr Goss:** Well, I agree.

**Dr Goncharova:** I'll just comment very briefly. Yes, I do feel hopeful. I agree with what Tim summarized. I also want to add that I feel hopeful because the pulmonary hypertension field is a very collaborative field. Basic scientists and clinical researchers work close together or sometimes it's even the same person who translates basic science to clinical trials. Having such collaborative environment and many translation-oriented researchers in the pulmonary hypertension field is very, very beneficial. And another reason why I feel hopeful is that our field is doing really good job in helping the next generation to grow. I am amazed by the progress shown by junior researchers at this Conference.

**Dr Goss:** I agree with Tim and Elena, that I think overall, the trajectory here is very hopeful and certainly optimistic for the future for pulmonary hypertension. I think, too, though, a Conference like this really makes you recognize the challenges and the hurdles that lie ahead. I say that because as we went through each of these different sessions, and several times it was brought up the amount of progress that's been made in the last decade for pulmonary hypertension. We now have, what's the count, 14 therapies for pulmonary hypertension? When there used to only be one in the late '90s. So I think when you look at where we've come from, we've made an incredible amount of progress. And the challenge now is that there are multiple therapies and we need better ways to fine-tune which patients will get the most benefit from which drug, whether that's taking a precision approach, individual patient cell approach, or something else. The other challenge is to figure out where the gaps are still—despite multiple drug classes available, where are there still gaps and the potential for new therapies to thrive? We have a relatively small patient population and pretty high standards now for what a clinical trial means. I think this is a challenge and is certainly a hurdle to bring new drugs to

market. But despite that, I'm certainly optimistic after these sessions at our group's ability to do that. Part of that comes from, as Elena was mentioning, just what a collaborative group it is. Programs like the PHA bringing everyone together at the same table make us believe that it's possible. And despite these challenges, we're going to continue to succeed. If you look at our trajectory over the last 10 years, to imagine where we could be 10 years from now is pretty outstanding if we continue this same course.

**Dr Lahm:** I think this is really where personalized medicine comes in. We are all interested in finding new pathways, and developing new drugs, and of course everybody's excited about that. But I really think the charge for the next 5 or 10 years will be to fine-tune therapies and to tailor regimens to individual patients and groups of patients. This could be accomplished with the help of things like genomics or wearables. But there are also other variables that we talked about at the Conference. For example, gender-specific differences come to mind, right? But also, Vinicio, you and I and some other colleagues talked about socially and economically disadvantaged patients. I think that's another important group that will benefit from the progress. We really need to make sure now that instead of finding a one-size-fits-all approach, we now focus our efforts on fine-tuning regimens for these individual groups. And again, this could be based on things like biomarkers or wearables or genomics. But also just general patient characteristics, such as income and social status and gender.

**Dr Tenorio:** I'm not as experienced as many of you in drug development and clinical trials but I believe that, compared to many other diseases, PAH is one of the rare diseases in which there are multiple drugs available. This certainly reflects how the approach to improve symptoms has been widely increased by the discovery of new pathways involved in the pathologic mechanisms of PAH. This is also leading to the discovery of molecules that target these mechanisms. However, these days it is much more difficult to do a clinical trial in PAH, because you have to prove that the new therapy is better that the currently available drugs and has a better response not only in 6MWD but also in the patient survival. I think we currently have 2 main challenges in drug discovery in PAH: 1) the identification of new molecular pathways involved in the disease development and 2) to develop molecules superior to the drugs that are currently in the market. As a scientist, that is both a challenge and a motivation.

**Dr de Jesus Perez:** Kara, there has always been this seeming divide between the adult and the pediatric world when it comes to pulmonary hypertension. In my mind, there's no reason why we shouldn't be able to apply what we learn in our studies to both adults and children. Did you see any particular aspects that may be uniquely tuned to pediatric PH that should be prioritized when thinking about how to push precision medicine forward in pediatrics?

**Dr Goss:** I think the need to bring adult and pediatric pulmonary hypertension providers to the same table speaks to how far we've come. We have gone from a time when there were few therapies available and children weren't surviving just a decade ago, to now we have patients on long-term therapy and children who are reaching adolescence, early adulthood. The fact that we're even talking about transitioning to adult pulmonary hypertension clinics is a testament to how far we've come! Certainly, there are things that are going to be unique to the pediatric population. There's much more regenerative capacity and growth capacity in kids who may get diagnosed with pulmonary hypertension relatively early in life. And what that means long term is really not clear; how that affects a developing or a young heart and its adaptive capabilities, when the RV is what typically determines survival long term, is really not well understood. Unlike adults, children have the ability to grow and with that, their lungs and their vasculature develop and grow, as well. So they continue to vascularize, despite having pulmonary hypertension. They may never do it to the degree of a child or adolescent without pulmonary hypertension, but they certainly have some unique recovery capabilities that adults don't have. I don't think we've really looked into how we harness that capacity—how we utilize that to help them recover from their disease, or even how we could apply that to adults with pulmonary hypertension. Another thing that I'd say is there's a lot more interest in the pediatric population than what I've seen so far in the adult population in transition, particularly for patients who need early IV therapies, to get them back off of IVs and onto orals. I think that's for multiple reasons. Certainly, the risks of having long-term indwelling catheters or even subcutaneous pumps for kids is higher than in adults. Their ability to dislodge a pump or develop a complication from their line is certainly much greater. So there are unique challenges that are within the pediatric population where there's some overlap, but I think there's a lot more to be learned about how we deal with pediatric pulmonary hypertension specifically, now that many more of them are surviving long term.

**Dr Tenorio:** I would like to add to Kara's comment that the molecular mechanisms of idiopathic PAH are not completely the same as those in adults. There are a lot of different reports highlighting the difference in the frequency of the mutation in the genes involved in PAH, and it affects directly how we understand the disease. As we know, *BMPR2* is a main actor in PAH, but we also know that there is another secondary actor with high importance in the pathophysiology of PAH. As an example, the frequency of mutations in a gene known as *TBX4* have been seen to be higher in pediatric population than in adults. So, I want to remark how important is to study not only adult mechanism underlying PAH but also to have in mind that it could be different in the pediatric population.

**Dr de Jesus Perez:** Thank you. So before we wrap up, I wanted to ask the group one final question: what do you want to see in the next PHA Scientific Sessions?

We talk about these wonderful possibilities, some of which are already being used for pulmonary hypertension, others are in process. But of all the things that we saw this year, what do you think will be the one that will likely become a big part of the way we diagnose and care for patients with pulmonary hypertension, so that maybe in 2 years when we have our next scientific session, we will probably see it as now being a cornerstone of what we do in our scientific and clinical scene?

**Dr Lahm:** Oh boy, that's an interesting question. So I'm looking at this aspirationally and will therefore go out on a limb. I can think about 2 things. We heard a lot about PVDOMICS. I think it would be terrific if we could hear something profoundly new about PAH that we didn't know before, based on PVDOMICS. Maybe a first step toward a new classification system or a new way about selecting people for a specific treatment. I think it would be amazing to learn something profoundly new about how we think about PAH. And PVDOMICS certainly can answer that question. I know it's ambitious, but hopefully in 2 years we'll know a little bit more about phenotyping and treatment responses. And the other thing I would like to see is some evidence that personalized medicine really improves outcomes. I think this would be a huge step forward. I think we all have high expectations for personalized medicine. But at the end of the day, at this point, there are not a whole lot of data. We are starting to move into that field and the study by Evangelos Michelakis, looking at DCA responses based on patients' genomic profiles, is a terrific step in that direction. So I think I really would like to see more evidence that personalized medicine really improves outcomes.

**Dr Goncharova:** Most of our studies are focused on pulmonary arterial hypertension, which is a rare disease. There are pulmonary hypertension groups that include a lot of patients: for example, a pulmonary hypertension that is secondary to heart failure with preserved ejection fraction. Do we want to focus one session on different forms of associated pulmonary hypertension?

**Dr de Jesus Perez:** Anybody else?

**Dr Tenorio:** For me, it was a wonderful coverage of a broad range of topics by different renowned speakers. Just to add an idea, based on precision medicine, pharmacogenomics has become a very important term to refer to the different responses to a therapy based on a genotypic profile. Maybe the importance of this issue can take more strength. Also, as Tim said, we are all intrigued about what PVDOMICS can add to the understanding of the disease.

**Dr Dai:** I can talk about my expectation and what I want to see in the next PHA Scientific Sessions. My idea of the research will be employing those novel techniques I learned about in the PHA Scientific Sessions. I saw several groups doing single-cell RNA sequencing and also mass spectrometry. I think these kinds of technology will be very helpful for the future to study the mechanism of the disease development. I would also like to see if there are potentially very novel therapeutic options and also some of those agents like FDA-approved drugs repurposed for pulmonary hypertension, such as DCA. These are 2 things I'm very excited to see in the future.

**Dr de Jesus Perez:** Good. How about you, Kara?

**Dr Goss:** I was trying to think of what will be a game-changer and will be increasingly used in the next couple of years. I hope with Tim and Elena, too, that the PVDOMICS initiative will really enlighten how we think about pulmonary hypertension and help us understand non-Group 1 pulmonary hypertension better, so we can target those diseases, too. I think that the implantables will become more readily available, so that might be one thing that we see 2 years from now. It's a little hard to think what will be mainstream 2 years from now, because that's pretty quick turnaround. But 5 years from now, 10 years from now, I do think a lot of these 'Omics approaches or more personalized-based approaches may really direct how we care for individual patients.

**Dr de Jesus Perez:** Alrighty. Well, I think this was a great roundtable discussion. I think we were able to really touch on many of the highlights. Thank you so much, guys, for taking the time to participate in the roundtable today. It was a real pleasure to share this with you. And I think if anything, I'm very excited about what the future will bring to the field. So I hope to see you guys in 2 years at our next meeting. Thank you all.

**Dr Lahm:** Thanks, Vinicio. I would like to see you sing and dance in 2 years.

**Dr de Jesus Perez:** Oh, I will. You know that I will. You go to ATS this year, you'll see me dancing (laughter). Thanks, everyone.