The pathway to breakthrough therapies...

This meeting will focus on promising therapies in clinical development, new targets, and changes in clinical trial designs that can lead to successful clinical trials and faster drug approval.

The faculty includes world renowned academic experts and members of the FDA.

9-10 July 2018 // Hyatt Regency Hotel, Bethesda, USA
A few comments from those who attended our symposium in 2017...

“Excellent meeting. Very honored to be invited. Really good, frank discussions of clinical trial design, new therapeutics that benefited from industry, research and clinical input.”

“A fantastic event, very interesting, relevant and inspiring!”

“Excellent conference. Learned a lot about state of advances in the field.”
Welcome to our 5th Annual Drug Discovery & Development Symposium for Pulmonary Hypertension

The Drug Discovery & Development for Pulmonary Hypertension Symposium is held each summer to bring leading scientists in the fields of pulmonary vascular disease, right heart failure, and clinical trial designs together with the pharmaceutical industry and regulatory authorities to help identify the most promising treatments for future development.

For each meeting, we assemble a faculty with exceptional achievements and expertise, and choose topics at the cutting edge of science in areas specially promising for the development of novel therapies. Each topic is critically reviewed by an expert panel, and open dialogue allows each voice to be heard. Attendees will experience, directly from the world’s leading authorities, how novel therapies can be best developed from the bench all the way to the successful completion of clinical trials.

This symposium serves as a unique forum for stakeholders interested in the treatment of pulmonary vascular diseases and sharing of cutting-edge science with international thought leaders. For researchers involved in the treatment of pulmonary hypertension, this meeting should stimulate innovative ideas and new approaches. For the pharmaceutical and biotechnology industries that have an interest in pulmonary vascular diseases, right heart failure or orphan diseases, it is a meeting not to be missed. By design, the various sessions offered allow ample opportunity for interaction among colleagues, if not during the meeting itself, at the social gathering of the evening reception.

We are indebted to our organizers Drs. Stuart Rich, John Newman and Brad Maron for a great program and to each of our speakers and chairpersons.

“Consider adding formal breaks to enhance networking opportunities.”

“Enjoyed the symposium immensely. Liked the format; exceedingly effective and useful for debates. The presentations and participants were very active and this is a strong positive aspect.”

...the pathway to breakthrough therapies!

Professor Paul Hassoun
President 2018/19, Johns Hopkins School of Medicine, USA
Dr. Stuart Rich is one of the world’s most recognized experts on pulmonary vascular diseases. For more than three decades he has dedicated his research and clinical efforts to finding better solutions for pulmonary hypertension.

Dr. Rich completed his residency training in medicine at Washington University in St Louis, and fellowship in cardiology at the University of Chicago. His career began at the University of Illinois where he was principal investigator for the National Institutes of Health (NIH) Registry on Primary Pulmonary Hypertension, the first of its kind, and has been the leader of the largest clinical centre in the US for evaluating and treating patients with pulmonary hypertension since 1980. Dr. Rich has conducted cutting-edge research on the molecular mechanisms, epidemiology, clinical presentation, natural history and treatments of the disease and been at the forefront of the development of virtually every new treatment for pulmonary hypertension, as well as the use of therapeutic procedures and devices. His pioneering research has led to a greater understanding of all types of pulmonary hypertension.

He has published hundreds of clinical articles and book chapters on pulmonary hypertension and is a founding member of the Pulmonary Vascular Research Institute, a global health professional organisation committed to bringing advances in treating pulmonary vascular diseases to the world. In 2014, he received the Heart for Hope Legacy Award from the Pulmonary Hypertension Association and in 2015 he was awarded the Lifetime Achievement Award from the Pulmonary Vascular Research Institute.

Dr. Rich’s clinical interests include: pulmonary hypertension, pulmonary vascular disease, pulmonary thromboembolism, adult congenital heart disease, right heart failure and complex and rare forms of heart diseases.
John Newman

Dr. John Newman, together with Dr. James Lloyd, is co-founder of the Pulmonary Circulation Center at Vanderbilt Pulmonary Circulation Center, USA.

The centre has conducted a continuous clinical research program of phenotyping and genotyping patients with pulmonary hypertension for more than 30 years. Dr. Newman authored the New England Journal of Medicine paper, reporting the novel insights in BMPR2 and clinical presentation from the largest known family with heritable PH. He mentors and assists in the development of multiple fellows and faculty in studies of pulmonary hypertension, leading Vanderbilt to a large comprehensive pulmonary hypertension program spanning clinics, clinical trials and genomics and signaling studies. He is funded by NIH, together with Co-investigator Dr. Anna Hemnes, for studies in the metabolic syndrome through the NIH PO1 and the NIH PVDOMICS network.

Dr. Newman, together with John Phillips, is also Co-primary Investigator of the new Undiagnosed Disease Network at Vanderbilt, a multicentre program to diagnose ultra-rare diseases. He is President of the CMREF, a non-profit fund that conceived and supports the Pulmonary Hypertension Breakthrough Initiative (PHBI), which is a consortium that harvests PH lungs during transplantation and coordinates scientific studies on the tissues, DNA, cells and fluids from these lungs. Dr. Newman and Dr. Rizwan-Hamid found the variant in HIF2a that causes Brisket disease in cattle, a form of high altitude pulmonary hypertension.

Bradley Maron

Dr. Maron is an Assistant Professor of Medicine at Harvard Medical School, Associate Physician in the Division of Cardiovascular Medicine at Brigham and Women’s Hospital and Co-director of the Pulmonary Vascular Disease Center at the Boston VA Healthcare System.

His laboratory focus involves characterizing the molecular mechanisms underpinning adverse pulmonary vascular remodeling in pulmonary arterial hypertension (PAH). Specifically, Dr. Maron demonstrated that pathophysiologically relevant concentrations of the hormone aldosterone induce reactive oxygen species accumulation in pulmonary artery endothelial cells, which oxidises a critical cysteinyi thiol redox switch to impair nitric oxide synthesis and promote collagen deposition in vitro and vascular fibrosis in vivo.

Dr. Maron reported on the translational relevance of these observations by identifying diminished cardiac output in PAH as a novel hemodynamic profile associated with increased pulmonary arterial aldosterone levels, and that aldosterone levels correlate with adverse cardiopulmonary hemodynamics in PAH patients. In addition, he has co-authored over 60 scientific manuscripts and is the lead editor of a recently published textbook on pulmonary vascular disease. The NIH, American Heart Association, PVRI, and various foundations, including the Cardiovascular Medical Research and Education Foundation (CMREF), Lerner Family Foundation and Klarman Family Foundation, fund his research.

Dr. Maron is also the recipient of numerous awards and honors such as the distinguished Eleanor and Miles Shore Scholar in Medicine and the Harvard Medical School Excellence in Teaching award.
Day 1 // Session 1

Monday 9 July 08:30 - 13:00

Repurposing novel drugs for pulmonary hypertension
Chairman: Stuart Rich
Panelists: Edda Spiekerkoetter, Harrison Farber

08:30 - 09:30
Repositioning existing drugs for rare diseases: Opportunities and challenges
• Speaker: Bruce Bloom

09:30 - 10:30
Dichloroacetate for pulmonary arterial hypertension
• NCT01083524
• Sponsor: University of Alberta
• Used as a treatment of lactic acidosis
• Speaker: Evangelos Michelakis

10:30 - 11:00
Break

11:00 - 12:00
Pilot study of anakinra in pulmonary arterial hypertension
• NCT03057028
• Sponsor: Virginia Commonwealth University
• Interleukin-1 receptor antagonist approved for rheumatoid arthritis
• Speaker: Dan Grinnan

12:00 - 13:00
Systems pharmacology to identify new targets for existing medications for pulmonary hypertension and RV failure
• Speaker: Joseph Loscalzo

13:00 - 14:00
Lunch
Repurposing existing drugs for rare diseases: Opportunities and challenges

Bruce Bloom

This presentation will discuss drug and other repositioning for rare diseases. Drug repositioning for orphan diseases has many challenges, including pharmacological, computational, clinical, financial, commercial and reimbursement issues.

Many of the repositioned drugs currently in the market for orphan disease were found through serendipity. Serendipity will continue to play a role in rare repurposing, we are now able to identify in an earlier or more systematic fashion the underlying mechanism ‘connecting’ drugs and diseases by sifting through bioinformation, discovering and utilizing “omic” information, and combining it with individual and group patient information from registries, EHRs and other sources.

This presentation will quickly discuss some rare repurposing successes, and then shift to looking at the current opportunities for repurposing, and the challenges of finding, reviewing, ranking, financing, undertaking, and completing rare disease repurposing research, and moving successes to market.

Dichloroacetate for pulmonary arterial hypertension

Evangelos Michelakis

Pulmonary arterial hypertension (PAH) is a progressive vascular disease with a high mortality rate. It is characterized by an occlusive vascular remodeling due to a pro-proliferative and anti-apoptotic environment in the wall of resistance pulmonary arteries (PAs). Proliferating cells exhibit a cancer-like metabolic switch where mitochondrial glucose oxidation is suppressed, whereas glycolysis is up-regulated as the major source of adenosine triphosphate production. This multifactorial mitochondrial suppression leads to inhibition of apoptosis and downstream signaling promoting proliferation. We report an increase in pyruvate dehydrogenase kinase (PDK), an inhibitor of the mitochondrial enzyme pyruvate dehydrogenase (PDH, the gatekeeping enzyme of glucose oxidation) in the PAs of human PAH compared to healthy lungs. Treatment of explanted human PAH lungs with the PDK inhibitor Dichloroacetate (DCA) ex vivo activated PDH and increased mitochondrial respiration. In a 4-month, open-label study, DCA (3 to 6.25 mg/kg b.i.d.) administered to patients with idiopathic PAH (IPAH) already on approved iPAH therapies led to reduction in mean PA pressure and pulmonary vascular resistance and improvement in functional capacity, but with a range of individual responses. Lack of ex vivo and clinical response was associated with the presence of functional variants of SIRT3 and UCP2 that predict reduced protein function. Impaired function of these proteins causes PDK-independent mitochondrial suppression and pulmonary hypertension in mice. This first-in-human trial of a mitochondria-targeting drug in iPAH demonstrates that PDK is a druggable target and offers hemodynamic improvement in genetically susceptible patients, paving the way for novel precision medicine approaches in this disease.

Interleukin-1 receptor blockade with anakinra in patients with pulmonary arterial hypertension

Dan Grinnan

Inflammation has long been implicated in the pathophysiology of pulmonary arterial hypertension (PAH). Inflammatory mediators are found in the vasculature of patients with familial and idiopathic PAH, high levels of inflammation are associated with worse survival in PAH, and several conditions that increase the probability of developing PAH (connective tissue disease, schistosomiasis, HIV) are highly inflammatory. It is suspected that anti-inflammatory therapy could reverse the vascular remodeling found in PAH, and this knowledge has given rise to attempts to suppress inflammation in patients with PAH. At present, a multi-center study using rituximab in patients with CTD-PAH is concluding, while tacrolimus is being further investigated for its anti-inflammatory and immunomodulatory properties.

The most common genetic predisposition to PAH, BMPR2 deficiency, has recently been linked to the inflammatory pathway. In a murine model, BMPR2 deficient mice treated with IL-1B developed significant pulmonary vascular remodeling. BMPR2 deficiency has also been linked to the estrogen pathway, potentially explaining the increased risk of developing PAH in women. Anastrazole is currently being evaluated as a promising therapy for PAH through alteration of estrogen metabolites and potential modification of pulmonary vascular remodeling. This collective information indicates that estrogen metabolites, through induced BMPR2 deficiency, may cause accelerated pulmonary vascular remodeling in the setting of high IL-1 levels.

Interleukin-1 (IL-1), the “fever molecule,” has long been known as a vital regulator of inflammatory pathways in humans. Not surprisingly, IL-1 has been shown to be elevated in patients with PAH. Furthermore, blockade with IL-1 receptor antagonists had protective effects against the development of PAH in an inflammatory animal model of PAH. To date, there are no clinical studies using IL-1 receptor antagonism in patients with PAH. However, Drs. Abbate and Trankle have evaluated the effects of anakinra in patients with various left ventricular conditions associated with inflammatory states. For example, in patients with recently decompenated congestive heart failure, daily administration of anakinra was associated with improved peak VO2 over 12 weeks. Similarly, patients with recent myocardial infarction were less likely to develop congestive heart failure after receiving anakinra. Collectively, this data suggests that anakinra should be evaluated in patients with PAH.

Our present and ongoing pilot study seeks to enroll 10 PAH patients in an exploratory analysis. In this open label study, patients receive 2 weeks of daily anakinra (100mg) injections. Data collected before and after treatment includes echocardiogram, cardiopulmonary exercise testing (CPET), biomarker analysis, and quality of life. Enrollment has only recently begun, and 5 patients have completed the protocol to date, and others are either actively participating or anticipating participation. While it is impossible to make assertions or conclusions from such a small sample size, our interim analysis on the initial 5 patients are encouraging.
We found that anakinra was well tolerated, with no adverse events to report. Anakinra is associated with reduced interleukin-6 (IL-6) and C-reactive protein (CRP) levels, showing that treatment with anakinra is likely to result in reduced levels of inflammation in patients with PAH. Decrease in IL-6 is significantly associated with improvement in anaerobic threshold (on CPET). Changes in IL-6 on treatment are significantly associated with changes in peak VO₂ (r = -0.975, p = 0.005), and trends toward improvement in quality of life (r = -0.725, p = 0.165). Decrease in CRP is trending toward an association with increased VO₂ (r = -0.800, p = 0.104), anaerobic threshold (r = -0.800, p = 0.104), and quality of life (r = -0.707, p = 0.182).

While our pilot study is not expected to make definitive conclusions about the overall role of IL-1 antagonism in PAH, we are highly intrigued by the current findings and feel that further investigation will be warranted. We anticipate using the insights from this pilot study to inform the development of a larger placebo-controlled clinical trial assessing the role of IL-1 blockade in patients with PAH.

References
1. Soon E et al. Elevated levels of inflammatory cytokines predict survival in idiopathic and familial pulmonary arterial hypertension. Circulation 2010;122(9):920-927

Systems pharmacology to identify new targets for existing medications for pulmonary hypertension and RV failure

Joseph Loscalzo

Conventional drug development suffers from an excess of reductionism. Characterizing a specific drug target in isolation reinforces the oversimplified Ehrlichian view of a single ‘magic bullet’ for every disease.

Systems and network approaches have begun to move this severely limited strategy to the more holistic paradigm of systems pharmacology. In this unbiased approach, pathways within disease subnetworks of the comprehensive protein-protein interactome are identified that govern disease phenotype (specific disease module), and one or more potential drug targets within it are identified and characterized.

The consequences of drug-target interactions on relevant pathways within the subnetwork that likely influence disease phenotype are then assessed. Network medicine and systems pharmacology offer the opportunity not only to identify novel therapeutic targets, but also to determine novel uses for pre-existing drugs (repurposing), to develop rational polypharmaceutical therapies, and to predict potential adverse effects in a comprehensive, unbiased way. Applications of these principles to the cardiopulmonary system and implications for the therapy of pulmonary hypertension will be discussed.
ACE2 therapy in pulmonary arterial hypertension

Anna Hemnes

Although the renin-angiotensin-aldosterone system is known to be activated in PAH, trials of angiotensin converting enzyme (ACE) inhibitors in this disease have not demonstrated benefit, and although AT-1 receptor antagonism appears to be beneficial in the monocrotaline rat model of pulmonary hypertension, this drug class has not been trialed in humans with PAH. The observation has led to the hypothesis that alternate hydrolysis of AngII to Ang-(1-7) via angiotensin converting enzyme 2 (ACE2) may be a more effective therapeutic intervention. Ang-(1-7) activates the Mas receptor (Mas1), which is present on endothelial cells and has vasodilatory, anti-inflammatory and anti-fibrotic effects, functionally antagonizing the effects of AT1 receptor stimulation. Finally, activation of the ACE2-Ang-(1-7) axis reduces oxidant stress in diabetes mellitus, suggesting impact on pathways of relevance to PAH. Thus the ACE2-Ang-(1-7)-Mas1 axis may be a promising therapeutic pathway in PAH.

We and others have demonstrated that both infusion of ACE2 and direct activation of Mas1 ameliorate rodent models of PAH likely through improved cytoskeletal function, which is consistent with prior work on ACE2. Further, the ACE2-Ang-(1-7) axis has been studied in a right ventricular (RV) failure model in which ACE2 peptide administration resulted in reduced RV hypertrophy and fibrosis improved function, suggesting potentially beneficial effects on both the pulmonary vasculature and also RV load stress responses. ACE2 enzymatic activity can be augmented by administration of an intravenous formulation of soluble recombinant form of the naturally occurring enzyme rhACE2 with existing safety data in healthy volunteers and ARDS (GSK2586881).

We tested the hypotheses that ACE2 activity is reduced in human PAH compared with healthy controls and that short term ACE2 administration may be safe in a proof of concept pilot study of GSK2586881 in PAH patients. We further sought to identify short-term markers of mas1 activation, suggesting molecular drug effect, which may facilitate future studies of mas1 activation in PAH.

PAH is characterized by reduced ACE2 activity. Augmentation of ACE2 in a pilot study was well-tolerated, associated with improved pulmonary hemodynamics and reduced markers of oxidant and inflammatory mediators. Targeting this pathway may be beneficial in human PAH.
**PB 1046, a VPAC2-specific VIP receptor agonist for PAH**

James White

Vasoactive intestinal peptide (VIP) related signaling may be depressed in patients with PAH, and this peptide has been of therapeutic interest in our field for 20 years. VIP is a 28 amino acid neuropeptide that activates VPAC1 and VPAC2 receptors in the pulmonary vasculature and has been shown to relax pulmonary vascular smooth muscle, antagonize pulmonary vasoconstrictors, and inhibit pulmonary vascular smooth muscle cell proliferation. The native peptide has a half-life of < 60 seconds, and a previous therapeutic attempt with an inhaled formulation did not achieve pharmacologically relevant, sustained plasma concentrations. PB1046, a novel sustained-release VIP analogue, is a recombinant 634 amino acid fusion protein comprised of a modified, biologically active VIP at the N-terminus and a physiologically inert repeating polymeric elastin-like peptide (ELP) at the C-terminus. PB1046’s VIP sequence was modified to reduce VPAC1 binding which should reduce gastro-intestinal activation and potential side effects like nausea and diarrhea. The ELP moiety significantly enhances in vivo exposure by creating a gel which protects the peptide at the center while allowing for sustained release at the edges of the subcutaneous drug depot. The inert, ELP drug delivery system has been tested therapeutically in hundreds of research participants with diabetes. In previous Phase 1 studies, PB1046 had a favorable safety profile in patients with hypertension and heart failure reduced ejection fraction. The PK profile supported weekly subcutaneous injection and investigators observed the expected, dose-dependent reduction of systemic blood pressure in these patient populations. GI side effects were not troublesome, and injection site reactions were mild to moderate. Previous studies have suggested the upregulation of VPAC2 in patients with PAH, and we hypothesize that PB1046 would relieve pulmonary vasoconstriction and improve cardiac output at doses that cause modest if any reduction in systemic blood pressure.

To evaluate the potential benefit of PB1046 in subjects with PAH, the sponsor is currently evaluating the safety, PK, and pharmacodynamic effects of PB1046 in an open-label, uncontrolled, multi-dose pilot study of PB1046 in PAH patients who have a permanently implanted hemodynamic monitor (cardioMEMS). In this pilot study, Ray Benza and his team at Allegheny Health have administered PB1046 subcutaneously once weekly for 8 weeks at escalating doses (0.2 mg – 1.0 mg) previously tested in the above noted Phase 1 studies. To date, 3 PAH patients with the CardioMEMS device have been enrolled. The first 2 subjects have completed the initial 8 weeks of PB1046 treatment, achieving the maximal dose level of 1.0 mg/kg. There have been no related serious adverse events (SAEs) or episodes of symptomatic hypotension or syncope reported to date. PB1046 appears to be well tolerated; both subjects rapidly dose titrated to the maximal dose level with only mild-moderate injection site erythema (redness) reported. The PK profile of treated subjects confirmed a linear, dose-related (but not dose proportional) increase in study drug exposure as observed in previous studies. As assessed using the CardioMEMS hemodynamic monitoring system, PB1046 was associated with reductions in mean pulmonary artery (PA) pressure and total pulmonary resistance; we observed increases in stroke volume and cardiac output without an increase in heart rate. Because both subjects reported subjective improvement in symptoms, the study protocol was amended to enable extended treatment. The first subject has been treated for approximately 20 weeks, and the second patient continues treatment currently, completing roughly 20 weeks to date. No significant safety events have been reported for either subject during extended dosing. A 3rd PAH patient has started treatment and is still undergoing dose titration, reporting mild-moderate injection erythema.

The preliminary data for PB1046 in the ongoing Phase I study in PAH patients are encouraging and support continued evaluation of PB1046 as a potential novel therapy for PAH patients. The FDA has now cleared a randomized, double-blind, parallel group Phase 2 PAH study assessing 16 weeks of PB1046 treatment for symptomatic PAH patients in the US who are on a background of endothelin antagonists and/or sGC stimulators/phosphodiesterase inhibitors. The comparator group is assigned a fixed, likely ineffective dose (0.2 mg; blindly titrating to the same dose) while the active group blindly titrates to maximally tolerated. The primary endpoint is change in PVR at week 16 with 6MW, NT-pro BNP, and symptoms as key secondaries. Twenty US centers are working on site initiation, and we plan on recruiting an additional 10 sites; we hope first participant will be dosed in July 2018.
It is time for clinical trials designed to treat patients with mild pulmonary hypertension who are symptom free

Evan Brittain and Robert Frantz

Historical perspective and emerging epidemiologic data
Pulmonary hypertension (PH) received a consensus definition in 1973 at the first World Symposium on Pulmonary Hypertension. On the basis of limited empirical data and no statistical analysis, PH was defined “arbitrarily” as 25mmHg with the recognition of a borderline range between 15-24mmHg. This definition has persisted for over 40 years. Since 1973, epidemiologic data have emerged to provide a more precise estimate of the distribution of pulmonary pressure in health and disease. The available data suggest that the normal mean pulmonary artery pressure (mPAP) is 14±3mmHg. Data from multiple small studies in selected populations suggest that mPAP values between 17-24mmHg (or corresponding echocardiographic estimates) are associated with adverse clinical outcomes. More recently, three large epidemiologic studies comprising over 31,000 subjects found that values between 17-24mmHg are associated with an elevated risk of all-cause mortality and hospitalization. Mild PH is common (~30% of subjects referred for RHC) and retrospective longitudinal data suggest many subjects with mildly elevated values progress to overt PH. Moreover, mild PH is associated with early right ventricular dysfunction. The weight of the evidence in favor of recognizing the clinical importance of mild PH across multiple disease states is overwhelming, but the implications for treatment remain unclear.

Treatment implications
The value of treating asymptomatic diseases is well-established in clinical medicine. Common examples include primary prevention of cardiovascular disease (hypertension, hyperlipidemia), prevention of symptomatic heart failure (Studies of Left Ventricular Dysfunction Prevention Trial), osteoporosis, and subclinical infections (HIV, hepatitis C). It is uncommon that PH is detected in truly asymptomatic individuals. The tests that measure pulmonary pressure (catheterization and echocardiography) are not performed on a population level but rather as clinically indicated. Nonetheless, targeting mild PH would mirror the management of clinical PH in which treatment is aimed at the underlying etiology.

The majority of mild PH occurs in subjects with underlying heart failure with preserved ejection fraction (HfPfEF). There are no established therapies for HfPfEF. Therefore, treatment of mild PH in HfPfEF would be directed at more aggressive management of risk factors for left heart disease. In addition to blood pressure and volume status, obesity and insulin resistance are potentially fruitful targets. These modifiable features of the metabolic syndrome are independent risk factors for mild PH. Obesity and insulin resistance improve with increasing physical activity, which is the only intervention to improve clinical outcomes in HfPfEF. Many clinicians are nihilistic with respect to the feasibility and sustainability of lifestyle modifications. Nonetheless, the safety, affordability, and efficacy (when adherence is maintained) of lifestyle interventions argue in favor of conducting clinical trials to reduce progression of HfPfEF related Group II PH and associated clinical outcomes. Recent advances in mobile health technology may facilitate large-scale physical activity interventions in this population.

Clinical trials in PAH without symptoms: Relevant considerations
Patients randomized to the placebo arm of successful PAH clinical trials who then enter active treatment extension phases tend not to achieve the same benefit of those who randomized to active treatment, supporting the value of proactive early intervention.

Symptoms in PAH are largely driven by inability to augment cardiac output during activity, and by right heart failure. Misattribution of PAH symptoms (deconditioning, obesity, anxiety) by patients and providers alike is common. Following diagnosis, many patients realize they were symptomatic long before they actively recognized symptoms. In addition, basal activity levels vary tremendously. Depending on activity profile, a new PAH patient may first become aware of symptoms during high altitude sojourn or when it becomes a challenge to walk to the mailbox. Accordingly relying on symptoms to guide entry for clinical trials appears foolish.

For rise in resting mPAP to occur, it is estimated that 60% of the microcirculation is impaired. Available treatments for PAH have anti-proliferative, anti-fibrotic and anti-inflammatory effects in animal models, and these effects may in part be responsible for their benefit in patients. Current trends toward targeting these aspects of the disease will be facilitated by moving away from symptoms and toward measurable vascular impact as endpoints in drug discovery. Pre symptomatic identification and treatment of pulmonary vascular disease may delay progression to the symptomatic state and subsequent right ventricular failure.

A concern is the feasibility of conducting clinical trials in asymptomatic patients. For a clinical endpoint driven phase III trial, this is surely a valid concern, since asymptomatic patients with PAH are uncommon, and time to clinical events relatively long. However, some high-risk groups with mild PH may be good candidates for treatment trials, including patients with connective tissue disease, HIV, BMPR2 mutation carriers, or those with a family history of PAH. In addition, innovative strategies such as use of cardiopulmonary exercise testing, PVR, imaging, and NT-proBNP as surrogate endpoints, potentially as an embedded component of a larger clinical trial including both symptomatic and asymptomatic patients, may be feasible.
New approaches in clinical trials for pulmonary hypertension and RV failure
Chairman: John Newman
Panelists: John Ryan, Dunbar Ivy

08:00 - 09:00
Regulatory viewpoint: The current challenges of conducting clinical trials for pulmonary hypertension in pediatric patients
• Speaker: Christine Garnett (FDA)

09:00 - 10:00
A novel imaging biomarker for pulmonary vascular disease
• PET-CT imaging with [89Zr]-bevacizumab
• a novel nuclear tracer to identify evidence of early pulmonary vascular injury in at-risk patients
• Speaker: Paul Yu

10:00 - 10:30
Break

10:30 - 11:00
Neladenoson bialanate in patients with chronic heart failure with preserved ejection fraction (PANACHE)
• NCT03098979
• Sponsor: Bayer
• Prodrug of adenosine A1 receptor agonist
• Speaker: Sanjiv Shah

11:30 - 12:30
Special Topic: Mechanical approaches to the treatment of pulmonary hypertension in advanced patients with right heart failure
• Speaker: Jonathan Rich

12:30
Adjourn

Regulatory viewpoint: The current challenges of conducting clinical trials for pulmonary hypertension in pediatric patients
Christine Garnett

Eleven drugs have been approved for the treatment of PAH in adults; however, to date, only one has been approved in the U.S. for the treatment of PAH in children. Although there is widespread recognition that treatments are needed for children with PAH, it has been difficult to conduct trials in this population. One reason that has been cited is the lack of clinical equipoise once a new treatment is approved for adults and used extensively off-label in children. Moreover, clinical practice guidelines for pediatric PAH recommend similar treatment strategies that are used in adults despite the lack of randomized clinical trials of the same therapies in children. Another challenge has been identifying feasible and reliable endpoints for demonstrating efficacy in children. The 6-minute walk test (6MWT) is a submaximal exercise test has been used in most drug development programs to establish the efficacy of new therapies for PAH in adults. The 6MWT is not appropriate for all children with PAH for reasons of reliability. Clinical trials of recently approved drugs in adults (macitentan and selexipag) used a composite endpoint of morbidity and mortality outcomes to demonstrate efficacy. Using a similar type of endpoint in pediatric trials may not be feasible, if it requires a large trial and long duration of follow-up to observe events. Therefore, novel approaches to both trial design and endpoints are needed to evaluate efficacy and safety of PAH treatments in children.

In drug development, pediatric extrapolation is defined as an approach to providing evidence in support of effective and safe use of drugs in the pediatric population when it can be assumed that the course of the disease and the expected response to the drug would be sufficiently similar in the pediatric and reference (adult or other pediatric) population. The U.S. FDA’s efficacy evaluation for bosentan relied on the findings in the BReATHe-3 trial, an open-label, uncontrolled study in 19 pediatric patients with PAH aged 3 to 15 years. This study’s findings of a reduction in pulmonary vascular resistance (PVR) were used to bridge the bosentan efficacy findings in adults to pediatric patients with PAH and support approval of the product for use in children. Although PVR obtained from right heart catheterization is now not used as an endpoint in pediatric trials due to an increase risk of serious adverse events with the procedure, the approach of extrapolating the efficacy from adults to children using a non-invasive biomarker is a pathway for evaluating the effectiveness of PAH drugs in children. This approach overcomes the challenge of conducting controlled trials using efficacy endpoints in these patients.
**PET-CT imaging with (89Zr) - bevacizumab:**
A novel imaging biomarker for pulmonary vascular disease

Paul Yu

**Introduction**
Pulmonary arterial hypertension (PAH) is a disease of progressive pulmonary vascular (PV) remodeling and obliteration with poor prognosis despite current therapies. Outcomes in PAH might be improved by earlier detection and intervention. Plexiform arteriopathy and neointimal lesions in human and experimental pulmonary hypertension (PH), and the enhanced expression of VEGF-A and other angiogenic growth factors suggest a process of dysregulated angiogenesis. We sought to validate VEGF-A as a non-invasive, PET-CT molecular imaging marker of PV remodeling in experimental PH.

**Hypothesis**
89Zr-bevacizumab and 89Zr-B.20, two radiolabeled anti-VEGF-A antibodies, can detect PV remodeling via PET-CT imaging in experimental PH and human PAH.

**Methods**
VEGF-A expression was examined by immunohistochemistry (IHC) in lung tissues of rats with PH, and explanted lungs of PAH patients. Experimental PH was induced in rats with 3 weeks of treatment with SU5416 and hypoxia (SU-Hx) treatment followed by 3 weeks of normoxia, or by treatment with monocrotaline (MCT) for 3 weeks. Rats with or without PH were injected with 0.2 mCi in 200 μg of 89Zr-bevacizumab or 89Zr-B.20 i.v., and scanned sequentially over 7 d. Sectioned lungs were analyzed by autoradiography and immunofluorescence. We are enrolling subjects with known PAH, exercise-associated PAH, and healthy subjects with no cardiopulmonary disease, and performing 89Zr-bevacizumab PET-CT imaging 7 d following i.v. administration of 1 mCi of 89Zr-bevacizumab.

**Results**
IHC using 3 distinct anti-VEGF-A antibodies revealed elevated VEGF-A expression in the intima and media of small pulmonary arterioles from PAH patients and SU-Hx rats. In vivo PET-CT imaging and ex-vivo autoradiography demonstrated enhanced 89Zr-bevacizumab retention in peripheral lung fields of SU-Hx rats vs. controls. Immunofluorescence confirmed enhanced retention of 89Zr-bevacizumab in the intima and media of remodeled small arterioles of SU-Hx rats. In preliminary analyses, we have detected retention of 89Zr-bevacizumab in the peripheral lung vasculature of individuals with PAH.

**Conclusions**
VEGF-A is a potential molecular imaging target in PAH, and 89Zr-bevacizumab is a potential PET molecular imaging probe for the non-invasive detection of PV remodeling.
Neladenoson bialanate in chronic heart failure with preserved ejection fraction (Panache)
Sanjiv Shah

HFpEF was previously thought of as occurring in the setting of significant LV hypertrophy and a preserved LVEF (> 45-50%) with LV diastolic dysfunction, resulting in left atrial and pulmonary venous pressure elevation. Eventually, these abnormalities led to right heart dysfunction and central venous congestion, resulting in the clinical syndrome of HFpEF.

It is now well known that there are multiple pathophysiologic abnormalities, both cardiovascular and non-cardiovascular, that occur in HFpEF. From a cardiac standpoint, there is likely a widespread microvascular dysfunction that involves all cardiac chambers. This microvascular dysfunction extends to other organs. In addition, LV systolic function is often abnormal; while global LVEF is preserved, longitudinal LV systolic dysfunction (reflecting the subendocardium) is frequently present and can be severe.

HFpEF is a syndrome that occurs due to marked "reserve dysfunction". Patients can seem fine at rest, but with exertion multiple abnormalities (cardiac, vascular, and peripheral [skeletal muscle]) begin to occur. This "reserve dysfunction" syndrome in multiple organs is likely often superimposed on other diseases such as pulmonary arterial hypertension, chronic lung diseases, and even HFrEF, leading to considerable morbidity and worse outcomes.

An ideal therapeutic for HFpEF would target several underlying pathophysiology related to multi-organ ‘reserve dysfunction’ with minimal effects on blood pressure or heart rate.

Neladenoson bialanate is an adenosine partial A1 receptor agonist that may improve mitochondrial function, enhance SERCA2a activity, optimize energy substrate utilization, reverse ventricular remodeling, and provide anti-ischemic cardioprotective effects without the adverse effects of full A1 receptor agonists (see figure 1).

PANACHE is a phase 2b, multi-center, parallel-group, dose-finding, randomized controlled trial that seeks to determine whether neladenoson is effective in patients with HFpEF. The primary endpoint on which the trial is powered is 6MWD, but a key aspect of PANACHE is a multi-domain endpoint approach for the evaluation of the drug: (1) QOL and exercise capacity (6MWD, KCCQ, physical activity); (2) cardiac function/remodeling (longitudinal strain, e’ velocity, E/e’ ratio, LA volume; TAPSE, RV s’ velocity); and (3) biomarkers (hs-troponin, NTproBNP). The trial also includes wearable-based data (Medtronic AVivo patch: accelerometry, ECG/telemetry, bioimpedance).

Beyond HFpEF, neladenoson could be a promising treatment for a variety of diseases (including PAH) that are associated with multi-organ ‘reserve dysfunction’.

Figure 1
Mechanical circulatory support for end stage pulmonary arterial hypertension

Jonathan Rich

Despite medical advances, pulmonary arterial hypertension (PAH) remains a progressive, incurable disease resulting in right ventricular failure and death. In fact, patients with PAH may remain alive for years in the face of long standing, systemic PA pressures so long as cardiac output is preserved. When overt RV failure ensues, however, there presently are no interventions other than lung transplantsations that have been shown to provide a durable treatment strategy. Unfortunately, the majority of patients with end stage PAH are either ineligible for transplantation or will die while waiting for a suitable donor.

Ventricular assist devices (VADs) have revolutionized the field of advanced left heart failure, providing durable ventricular support, either as a bridge to heart transplantation (BTT) or as a stand-alone, long term destination therapy (DT) treatment option. While not without potential for complications, current generation devices have proven to be durable and markedly improve both quality of life and survival in end stage left heart failure. Although commercially available, VADs are approved only for use as left ventricular assist devices (LVADs), such VADs may be configured for use as right ventricular assist devices (RVADs) and there exist many published reports of successful RVAD implants either in a BIVAD configuration or even as an isolated RVAD. The main caveat, however, is that the use of an RVAD in the face of significant pulmonary hypertension remains an uncharted venture.

This presentation will highlight the rationale, feasibility, and potential benefits of pursuing a strategy of RVADs for end stage PAH while also addressing the likely challenges and pitfalls that must be considered and overcome for this pursuit to prove successful.
Our Invited Faculty LISTED IN ALPHABETICAL ORDER

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WE LOOK FORWARD TO SEEING YOU IN BARCELONA!
Pulmonary Vascular Research Institute

We are pleased to announce that the first scientific meeting of the International Consortium for Genetic Studies in PAH (PAH-ICON http://www.pahicon.com) will be held in Barcelona, sponsored by the PVRI.

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