4th PVRI Annual Drug Discovery & Development Symposium for Pulmonary Hypertension
A few comments from those who attended our symposium in 2016...

“The meeting was fantastic...the presentations were first rate.”

“This was the finest scientific meeting on pulmonary hypertension I have ever attended.”

“The discussions were very provocative...perhaps the best part of the meeting.”

“What a great symposium...please let me know when next year’s meeting is.”
Welcome to our 4th Annual Drug Discovery & Development Symposium for Pulmonary Hypertension

The Drug Discovery and Development for Pulmonary Hypertension Symposium is held annually 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 in areas that will influence the development of therapies immediately. Each topic will be critically reviewed by an expert panel and open dialogue will allow your voice to be heard. Attendees will experience how novel therapies can best be developed towards successful clinical trials from the input of the world’s leading authorities.

This symposium serves as a unique forum for stakeholders interested in the treatment of pulmonary vascular diseases for the sharing of cutting-edge science with the input of international thought leaders.

For researchers involved in the treatment of pulmonary hypertension this meeting should stimulate new ideas and 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 that should not be missed. The meeting is designed to allow opportunities for interaction among colleagues during sessions and at the evening reception.

—I will be attending this meeting every year... people involved in developing therapies for pulmonary hypertension or right ventricular failure should not miss this.”

The pathway to breakthrough therapies...
Stuart Rich
Dr Stuart Rich is a Cardiologist and Director of Northwestern Medicine’s Pulmonary Vascular Disease Programme at the Bluhm Cardiovascular Institute and a Professor of Medicine, Northwestern University Feinberg School of Medicine, USA.

Dr Rich is one of the world’s most recognised 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 Loyd, is co-founder of the Pulmonary Circulation Center at Vanderbilt Pulmonary Circulation Center, USA.

The centre has conducted a continuous clinical research programme 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 programme spanning clinics, clinical trials and genomics and signalling studies. He is funded by NIH, together with Co-investigator Dr Anna Hemnes, for studies in the metabolic syndrome through the NIH P01 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 programme 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.

Ardeshir Ghofrani
Dr Ardeschir Ghofrani is Professor of Pulmonary Vascular Research at Justus Liebig University, Giessen, Germany and Head of the Pulmonary Hypertension Division at the University Hospital in Giessen, Germany.

Professor Ghofrani is also Director of Pneumology, as well as Medical Executive Director at the Kerckhoff Clinic in Bad Nauheim, Germany, and part-time Professor for Pulmonary Vascular Medicine at Imperial College, London.

He leads a translational research group on development of new therapeutics for cardiopulmonary vascular disease and is a member of the steering committee of the Excellence Cluster Cardio-Pulmonary System (www.eccps.de). He is also a founding member of the Pulmonary Vascular Research Institute (www.pvrinstitute.org).

He has participated in the development of several therapeutics for chronic lung diseases and pulmonary hypertension, including prostanoids, phosphodiesterase inhibitors, endothelin receptor antagonists, tyrosine kinase inhibitors and stimulators of the soluble guanylate cyclase.

Professor Ghofrani has received four awards for investigations in pulmonary vascular science, is a Fellow of the European Respiratory Society (ERS) and a reviewer for several medical scientific journals.
Monday 10 July 08:30 - 12:30

New Drugs for Pulmonary Hypertension Entering Clinical Trials
Moderator: John Newman
Expert Panel: Marion Delcroix, Nazzareno Galie

08:30 - 09:30
A Study of Ubenimex in Patients With Pulmonary Arterial Hypertension: The ‘LIBERTY’ Trial
- Inhibitor of Leukotriene A4 Hydrolase
- ClinicalTrials.gov NCT02664558
- Phase 2 (active)
- Sponsor: Eiger BioPharmaceuticals
- Presenter: Norbert Voelkel, VU University Medical Center

09:30 - 10:30
Tocilizumab in the Treatment of Pulmonary Arterial Hypertension (TRANSFORM-UK)
- Monoclonal Antibody Against the Interleukin-6 Receptor (IL-6R)
- ClinicalTrials.gov NCT02676947
- Phase 2 (open label)
- Sponsor: Papworth Hospital NHS Foundation Trust and Roche Pharma AG
- Presenter: Mark Toshner, University of Cambridge

10:30 - 11:30
ABI-009 for Severe Pulmonary Arterial Hypertension (WHO FC III and IV)
- mTOR Inhibitor (inhibits the mechanistic target of rapamycin)
- ClinicalTrials.gov NCT02587325
- Sponsor: Aadi, LLC, and University of Pittsburgh
- Presenter: Mark Simon

11:30 - 12:30
UPDATE: Tyrosine Kinase Inhibitors as a Treatment of Pulmonary Hypertension - Lessons Learned and Future Challenges
- Presenter: Ralph Schermuly, University of Giessen

12:30 - 13:30
Lunch

12:30 - 13:30
Held in Salon Humboldt
PVRI Pharma Task Force Breakout Session
Lunch included
- Presenter: Peter Fernandes see p.9 for full agenda

A Study of Ubenimex in Patients with Pulmonary Arterial Hypertension: The ‘LIBERTY’ Trial
Norbert Voelkel

The ‘LIBERTY’ trial, sponsored by Eiger Biopharmaceuticals Inc [Palo Alto, CA], is a proof of concept Phase 2 study to assess whether ubenimex (bestatin) decreases PVR, the primary endpoint, in WHO Group I PAH patients. The patients are randomised 2:1, ubenimex vs placebo in a 24 week double blind study. The rationale for choosing ubenimex is based on the results from preclinical studies [Tian W. et al, Sci Transl Med, 2013] and on inhibition of leukotriene A4 synthase (LTA4 synthase), the enzyme responsible for the synthesis of LT4 and possibly due to its anti-aminopeptidase activity. The preclinical studies demonstrated that LT4 levels were elevated in the lungs from severely pulmonary hypertensive athymic rats and that treatment of the animals with ubenimex prevented, and reversed, PAH. LT4 is chemotactic for neutrophils and in the above study was shown to cause endothelial cell (EC) apoptosis; in culture, inhibition of macrophage LT4 synthesis by bestatin prevented EC apoptosis. In this PAH disease model in rats that lack T lymphocytes, LT4 synthesis inhibition hypothetically interrupts the initial inflammatory trigger of pulmonary vascular macrophage activation and LT4 - dependent endothelial cell death. This mechanism is likely also contributing to the chronic pulmonary vascular inflammation.

A second mechanism of ubenimex action appears to be its ability to kill abnormal proliferating vascular lumen cells, and a third mechanism, so far not experimentally investigated in pulmonary hypertension models, relates to its aminopeptidase inhibiting properties. Inhibition of aminopeptidase has been shown to inhibit angiogenesis, and ubenimex is presently used in cancer patients to synergistically enhance the effects of chemotherapy.

In conclusion: The ‘LIBERTY’ trial repurposes the anti-cancer drug ubenimex to target the pulmonary vascular immune response and potentially angiobobliterative vascular remodelling.

Tocilizumab in the Treatment of Pulmonary Arterial Hypertension (TRANSFORM-UK)
Mark Toshner

Pulmonary arterial hypertension still carries a poor prognosis despite the therapeutic advances of the last 20 years. There remains an urgent need for the development of new treatments, particularly as the results from combination studies of vasoactive therapies has been, to date, mixed and arguably disappointing. The strong association of PAH with dysregulated immunity and inflammation has been established with autoimmune diseases, most prominently scleroderma, but also notably rheumatoid arthritis, SLE and MCTD. Auto-immune diseases are recognised as causally associated with PAH but there is also an association of IPAH with auto-immune thyroid disease, links to HLA subtypes and the presence of auto-antibodies. IPAH has previously been...
speculated to be an auto-immune disease. Within the pulmonary vascular lesions there is accumulation of inflammatory cells including T and B lymphocytes with altered T regulatory cell function. It is clear that inflammation and dysregulated immunity play a significant role in a spectrum of causes of PAH. From the perspective of identifying pathways that are targetable, IL-6 has emerged as a strong candidate. IL-6 is raised in peripheral blood and within the lung in PAH and is an independent marker of prognosis. Over-expression of IL-6 in animal models using transgenic mice leads to pulmonary hypertension and in hypoxia, IL-6 deficient mice are protected. Tocilizumab is an IL-6 receptor antagonist established as safe, well tolerated and effective, primarily in rheumatoid arthritis and has shown promise in scleroderma. We will explore the background rationale for IL-6 therapies and outline the trial design of the first phase 2 trial of tocilizumab in selected patients in group 1 PAH.

References

Increased proliferation and resistance to apoptosis of pulmonary vascular cells in small pulmonary arteries (PAS) is a key component of pulmonary vascular remodelling in PAH, and effective anti-proliferative remodelling-focused therapies are needed.

The mechanistic (formerly mammalian) target of rapamycin (mTOR) is a master-regulator of cell metabolism, proliferation and survival. mTOR acts through two functionally distinct complexes, mTOR complex 1 (mTORC1), which controls cell growth via p70 S6 kinase 1 (S6K1), and mTORC2 that activates Akt and reduces apoptosis. Recent studies from many research groups, including ours, have shown that both mTORC1-S6K1 and mTORC2-Akt are activated in vascular smooth muscle cells in small remodelled PAs (PASMC) in human PAH and experimental PH, which is required for glycolytic energy production, increased apoptosis resistance, cell proliferation, and pulmonary vascular remodelling. mTOR inhibition selectively reduces proliferation and induces apoptosis in human PAH PASMC, attenuates human PAH PA endothelial cell proliferation and neo-intimal occlusion of small PAs and reverses or regresses PH in animal models. Our new data show that mTOR inhibition reverses right ventricle (RV) cardiomyocyte hypertrophy and improves RV function in experimental PH. Together these findings strongly suggest potential attractiveness of mTOR inhibition as anti-proliferative remodelling-focused therapeutic strategy for patients with PAH.

Rapamycin is an allosteric mTORC1 inhibitor with strong anti-proliferative activity. It is approved by FDA for the prevention of graft rejection in kidney transplant recipients, as an anti-restenosis agent following balloon angioplasty in coronary arterial stents and for the treatment of pulmonary lymphangiolyomyomatosis, and is entered cancer clinical trials as an additive anti-proliferative agent. Rapamycin prevents development of PH in animal models and was well tolerated in pilot clinical trial for patients with idiopathic PAH and chronic thromboembolic pulmonary hypertension (CTEPH). The challenges of the rapamycin use in human PAH lie in its failure to promote apoptosis when given in clinically relevant doses and in clinical risks for adverse side-effects that include hyperglycemia, hyperlipidemia, insulin resistance, and increased incidence of new-onset type 2 diabetes and interstitial pneumonitis.

ABI-009 (nab-Rapamycin) is a long acting nanoparticle human albumin-bound formulation of rapamycin with improved penetration in lung tissue. ABI-009 has shown preferential accumulation in lung, improved effect on cell viability, strong antiproliferative activity in several pre-clinical tumor xenograft models and demonstrated significant anti-remodelling effects in porcine model of peripheral artery restenosis. ABI-009 was well tolerated in a phase 1 clinical trial in patients with solid tumors with evidence of responses in renal cell carcinoma and bladder cancer, both of which typically have up-regulated mTOR. Despite higher doses, the safety and pharmacokinetic profile compared favorably to oral rapamycin (historical comparison).

Based on pre-clinical evidence of improved lung accumulation, anti-remodelling potential and better safety profile, AADi, LLC and the University of Pittsburgh are initiating a clinical trial of ABI-009 as antiproliferative therapy for patients with severe PAH. This is a
phase 1 single arm, open-label dose-escalation study. Enrollees are 18 years or older with a current diagnosis of WHO Group 1 PAH, receiving background therapy and without other major comorbidities, e.g. heart or liver disease, malignancy, uncontrolled diabetes mellitus or hyperlipidemia. ABI-009 will be administrated once weekly for 16 weeks. The primary outcomes are maximum tolerated dose, dose limiting toxicities and safety profile of 16 weeks ABI-009 given IV. As secondary endpoints, pulmonary vascular resistance by right heart catheterisation, pulmonary artery pressure, pulmonary artery occlusion pressure, pulmonary capillary wedge pressure, and central venous pressure will be measured. Other metrics will include Doppler-echocardiographic assessments of right ventricular structure and function, six-minute walk distance, WHO functional class, and pulmonary function test. Exploratory objectives are to evaluate pharmacokinetic information that may be correlated with safety and/or efficacy observations. If effective, the ABI-009 dose for phase 2 study will be determined and phase 2 study will be planned.

UPDATE: Tyrosine Kinase Inhibitors as a Treatment of Pulmonary Hypertension - Lessons Learned and Future Challenges
Ralph Schermuly

Pulmonary arterial hypertension (PAH) is a disease of small pulmonary arteries that results in increased pulmonary vascular resistance and right heart hypertrophy. There has been enormous progress in the understanding of the mechanisms of pulmonary vascular remodelling that led to the introduction of vasoactive drugs like prostanoids, endothelin antagonists, and phosphodiesterase 5 inhibitors for treatment of PAH. These compounds either alone or in combination improve haemodynamics, exercise capacity, and survival of patients with PAH, but are not able to reverse the disease. Based on the observation that dysregulated proliferation, apoptosis, inflammation, and metabolism underlie pulmonary vascular changes, the functional importance of several new signalling pathways has been described in preclinical and clinical studies. Among them, the dysregulation of growth factors and their respective receptors in pulmonary vascular diseases gained attention. The binding of growth factors like epidermal growth factor, fibroblast growth factor, or platelet-derived growth factor (PDGF) to their corresponding receptor tyrosine kinase (RTK) activates a complex signalling network, which results in proliferation and survival of cells. With the introduction of RTK inhibitors in the field of cancer, the efficacy of these compounds was also investigated in nonmalignant diseases. In this line, the RTK inhibitor imatinib was shown to reverse experimental pulmonary hypertension (PH) via inhibition of PDGF receptor (PDGFR) and to improve hemodynamics in patients with PAH.

References
Day 1 // Session 2

Monday 10 July 13:30 - 17:30

Novel Drugs for Pulmonary Vascular Diseases Ready for Clinical Trials

Moderator: Ardeschir Ghofrani
Expert Panel: Jean-Luc Vachiery, Laura Price

13:30 - 14:30
KAR5585
• The Serotonin Hypothesis Revisited—Clinical Implications for TPH1 Inhibition
• ClinicalTrials.gov NCT02746237
• Phase 1 Completed
• Sponsor: Karos Pharmaceuticals
• Presenter: Mandy MacLean, University of Glasgow

14:30 - 15:30
MFC1040
• MIF inhibitor that Blocks Vascular Cell Proliferation and Perivascular Inflammation
• Orally Available, Small Molecule Antagonist of MIF
• Sponsor: MIFCARE
• Presenter: Marc Humbert, Université Paris-Sud

15:30 - 16:30
CXA-10 (10-nitro-oleic-acid) for Pulmonary Hypertension
• Modulator of Nrf2 and NF-κB,
• Phase 1 Completed, Phase 2 Planned
• Sponsor: Complexa Inc
• Presenter: Tanja Rudolph, University of Cologne

16:30 - 17:00
Inhaled Sodium Nitrite in Pulmonary Hypertension Associated with Heart Failure with Preserved Ejection Fraction
• ClinicalTrials.gov NCT01431313
• Phase 2 Trial Completed
• Sponsor: Mast Therapeutics and NIH
• Presenter: Marc Simon, University of Pittsburgh

17:30 - 17:45
Demonstration of the PVRI ‘Digital Clinic’
• Presenters: Martin Johnson, Colin Church, University of Glasgow

17:45 - 19:00
Cocktail Reception
The Serotonin Hypothesis Revisited—Clinical Implications for TPH1 Inhibition
Mandy MacLean

The serotonin hypothesis of pulmonary hypertension (PAH) arose after an outbreak of PH in patients taking the anorexigenic drugs aminorex and dexfenfluramine. These are serotonin transporter (SERT) substrates and indirect serotenergic agonists. There has been accumulating evidence over the last 20 years implicating serotonin in the pathobiology of PH. In human pulmonary arteries, serotonin is synthesised by tryptophan hydroxylase 1 (TPH1) in endothelial cells and acts at the 5-HT1B receptor and the SERT to mediate constriction and proliferation of pulmonary artery smooth muscle cells (PASMC). Serotonin has been shown to cause lung inflammation, apoptosis, fibrosis, PASMC migration, contraction and proliferation in models of PH. This makes inhibition of serotonin an attractive concept for PH treatment. Indeed of the over 700 papers published on the potential role of serotonin in PAH, less than 0.006% suggest that it does not play a pathogenic role. In the 1980s, the hypothesis was however somewhat dismissed because ketanserin, a 5HT2A antagonist, failed to reduce pulmonary pressures in PH patients and indeed caused systemic hypotension. However this approach was driven by the assumption that it is the 5HT2A receptor that mediated the effects of serotonin. Indeed, in rats, this is the case. However, in the human pulmonary artery it is the 5HT1B receptor in cooperation with the SERT, whilst only systemic arterial constriction is mediated by the 5HT2A receptor. Serotonin may also interact with the bone morphogenetic receptor type II (BMPRII) to provide a ‘second hit’ risk factor for hPAH. Proliferation to serotonin in hPASMCs is partly due to serotonin-induced, Nox-dependent oxidative stress. In hPASMCs, estrogen can upregulate TPH1, SERT and 5HT1B expression and in some models of PH, serotonin can cause pathogenic dysregulated estrogen syntheses. 5HT1B receptor expression is extremely highly upregulated in human distal hPASMCs from female PAH patients, in an oestrogen-dependent fashion, and mediates proliferation that can be reduced either by 5HT1B antagonists or microRNA96 which targets the gene for 5HT1B. Pharmacology dictates that to treat PH you would either need to inhibit both the SERT and the 5HT1B receptor together or inhibit serotonin synthesis. We are not aware of drugs that will inhibit both the 5HT1B receptor and SERT and so targeting serotonin through its synthesis is an attractive option. Several papers have demonstrated that TPH1 is the rate limiting step in the synthesis of peripheral serotonin and inhibition of this leaves the central effects of serotonin intact. Many studies have shown that inhibition of TPH1 has either protected or reversed experimental PH and that TPH1 knockout mice are protected against hypoxia-induced PH. PH patients with greater haemodynamic impairment show significantly reduced serotonin plasma levels after imatinib treatment compared with placebo and this has been attributed to imatinib-induced TPH1 downregulation via inhibition of PDGFR-B signalling. A very recent study convincingly demonstrates the effectiveness of the novel TPH1 inhibitor KAR5585 in the monocrotaline and sugen/hypoxic rat models of PH. This compound is reported to demonstrate a dose-dependent reduction in serotonin synthesis with excellent safety, tolerability and robust pharmacokinetics. Hence there is convincing evidence and some anticipation that TPH1 inhibition may be an effective new approach for the treatment of PH.

Preclinical Studies of a New Potent Orally Active Antagonist for the MIF-CD74 Axis in Development for Pulmonary Hypertension
Marc Humbert

Background: We have recently identified that macrophage migration inhibitory factor (MIF) and its signalling through CD74 are key players at the crossroad of inflammation, cancer-like phenotype and endothelial dysfunction in the pathogenesis of pulmonary hypertension (PH). Although several classes of small molecule MIF inhibitors have been described in the literature, none have yet been approved for clinical use. Therefore, we have designed and synthesised a new potent orally active antagonist, N-(phenylmethyl)-benzoxazol-2-thione 29, and herein we investigate its chronic pharmacological effect in PH in vitro and in vivo.

Methods and Results: We have used an integrated approach to screen 26 new bioactive compounds for their ability to attenuate DU-145 cell survival, a human cancer cell line that requires MIF-CD74 activated signal transduction pathways for their cell survival. The best response was achieved with the N-(phenylmethyl)-benzoxazol-2-thione 29, an observation that was replicated in vitro, with cultured pulmonary endothelial cells (ECs) from patients idiopathic PH exhibiting diminished sensitivity to apoptotic induction. Interestingly, we found a beneficial curative effect of chronic treatment with N-(phenylmethyl)-benzoxazol-2-thione 29 in two pre-clinical models of severe PH, namely monocrotaline (MCT) and the SU5416-hypoxia (SuHx) rat models. Compound 29 showed significant protective effect against PH as it delayed disease progression, decreased values of mean pulmonary arterial pressure, pulmonary vascular resistance, degree of pulmonary vascular remodelling and reversed right ventricular hypertrophy.

Conclusion: Our study demonstrates the in vitro and in vivo efficacy of N-(phenylmethyl)-benzoxazol-2-thione 29, a new orally bioavailable MIF/CD74 antagonist. Additional optimisation of activity and drug properties of this compound are ongoing.

Keywords: Inflammation; Pulmonary vascular remodelling; Cell survival; Migration inhibitory factor; CD74; Therapeutic innovation.

CXA-10 (10-nitro-oleic-acid) for Pulmonary Hypertension
Tanja Rudolph

Pulmonary arterial hypertension (PAH) is characterised by adverse remodelling of pulmonary arteries. Although the origin of the disease and its underlying pathophysiology remain incompletely understood, inflammation has been identified as a central mediator of disease progression. Oxidative inflammatory conditions support the formation of electrophilic fatty acid nitroalkene derivatives, which exert potent anti-inflammatory effects. The current study investigated the role of 10-nitro-oleic acid (OA-NO2) in modulating the pathophysiology of PAH in mice. Mice were kept for 28 days under normoxic or hypoxic conditions, and OA-NO2 was infused subcutaneously. Right ventricular systolic pressure (RVSPs) was determined, and right ventricular and lung tissue was analysed.
The effect of OA-NO2 on cultured pulmonary artery smooth muscle cells (PASMCs) and macrophages was also investigated. Changes in RVPsys revealed increased pulmonary hypertension in mice on hypoxia, which was significantly decreased by OA-NO2 administration. Right ventricular hypertrophy and fibrosis were also attenuated by OA-NO2 treatment. The infiltration of macrophages and the generation of reactive oxygen species were elevated in lung tissue of mice on hypoxia and were diminished by OA-NO2 treatment. Moreover, OA-NO2 decreased superoxide production of activated macrophages and PASMCs in vitro. Vascular structural remodelling was also limited by OA-NO2. In support of these findings, proliferation and activation of extracellular signal-regulated kinases 1/2 in cultured PASMCs was less pronounced on application of OA-NO2. Our results show that the oleic acid nitroalkene derivative OA-NO2 attenuates hypoxia-induced pulmonary hypertension in mice. Thus, OA-NO2 represents a potential therapeutic agent for the treatment of PAH.

Inhaled Sodium Nitrite in Pulmonary Hypertension Associated with Heart Failure with Preserved Ejection Fraction
Marc Simon

The most common form of pulmonary hypertension (PH) is that associated with left heart disease (Group 2 PH, PH-LHD), for which there is no approved therapy. Interventions specifically targeting patients with PH-LHD have had mixed results, in large part due to phenotypic heterogeneity. Of left heart diseases, heart failure with preserved ejection fraction (HFpEF) is perhaps the most prevalent and also suffers from a lack of specific therapies. Chronically elevated pulmonary venous pressures from left ventricular diastolic dysfunction may result in pathological pulmonary vascular remodelling and PH, referred to as PH with heart failure and preserved ejection fraction (PH-HFpEF). PH-HFpEF is associated with poor clinical outcomes and may represent a specific, targetable phenotype for developing therapies. Nitrite (NO2-) is an anion that is reduced to nitric oxide (NO), particularly during hypoxia and acidosis, with a half life of about 40 minutes. Preclinical and phase 1 studies indicate that exogenously administered nitrite is a potent vasodilator.

We performed a phase IIa safety and efficacy trial of the acute effects of an inhaled formulation of sodium nitrite on cardiopulmonary haemodynamics in PH-HFpEF patients (defined as mean pulmonary artery pressure ≥25, pulmonary artery wedge pressures [PAWP] >15, and transpulmonary gradient >12 mm Hg) as compared with WHO Group 1 PAH or Group 3 PH patients. Nebulised doses of 45mg and 90mg were administered sequentially and haemodynamics monitored for 1 hour after each dose. Thirty-six patients were enrolled (10 PH-HFpEF, 20 Group 1 PAH patients on background PH specific therapy, and 6 Group 3 PH). Drug administration was well tolerated. Nitrite inhalation significantly lowered pulmonary, right atrial and PAWP, most pronounced in patients with PH-HFpEF. There was a modest asymptomatic decrease in cardiac output and systemic blood pressure. Pulmonary vascular resistance decreased only in Group 3 PH patients. Pulmonary artery compliance increased substantially, particularly in patients with PH-HFpEF. There was a trend towards improvement in the resistance-compliance relationship in PH-HFpEF after the administration of inhaled sodium nitrite, associated with the decrease in PAWP. We have since enrolled an additional 5 PH-HFpEF patients with consistent results.

Inhaled nitrite appears safe acutely in PH patients and may be efficacious in PH-HFpEF and Group 3 PH primarily via improvements in left and right ventricular filling pressures and pulmonary artery compliance. The lack of change in PVR likely may limit efficacy for Group 1 patients. Currently there is a phase II trial of inhaled sodium nitrite in HFpEF and a phase II trial of an oral formulation in PH-HFpEF.
Precision Medicine Approach to Rare Disease Therapies

Krishna Prasad

Personalised medicine is a move away from traditional medicine (one size fits all approach) and to all patients affected by a disease regardless of specific differences in their genetic make-up. Precision medicine tailors medical treatment to the individual characteristics of each patient and allows identification of subpopulations that differ in their disease susceptibility or in their response to a specific treatment.

There have been several initiatives, collectively and independently, in many countries in Europe. The EMA has a lead role in bringing forward efforts to enhance delivery of safe and efficacious medicines across Europe while addressing multiple regulatory challenges, to support innovation and facilitate clinical trial methodologies. Within Europe, there is active regulatory engagement with personalised medicine/precision medicine concept and, efforts include scientific support for drug development, regulatory guidance, and protocol assistance for SMEs and stakeholders.

Regulatory aspects dealing with rare disease (orphan) therapies are complex with have geographically varied criteria for orphan designations. In Europe orphan designation are the remit of the Committee of Orphan Medicines (COMP). The recognition of molecular subtypes or genomic subpopulations in many disease entities provides new opportunities and challenges. Challenges include approaches that are agnostic to traditional disease classification or taxonomy but are mechanism based relating to molecular heterogeneity, genotype/phenotype interactions necessitating moving regulatory paradigms from conventional RCTs to use of adaptive design studies. The new clinical trial regulation (2016) and voluntary harmonisation procedure (for CTAs) have facilitated use of pragmatic clinical trials during development and enhanced use of novel trial designs such as basket and umbrella trials. With rare disease therapies, data generation in the context of drug development using small study populations or novel trial methodologies are at the forefront of discussion between the EMA committees and industry and stakeholders. The biomarker development aspects for rare diseases (and others) are aided by several guidelines generated by the working parties (SAWP, PGWP and CVSWP etc.). The biomarker qualification process (from SAWP/CHMP) aids development of BMs for use in the regulatory development programmes (endpoints or surrogates). The PGWP has provided several guidance documents for genomic biomarker and companion diagnostic developments, additionally publishing data demonstrating increasing number of genomic markers in development of approval of new therapies.

The EMA/CHMP have facilitated evaluation and approval processes in Europe to the use of small data sets and offer a number of opportunities. These include accelerated assessment to address unmet medical need, conditional marketing authorisations (CMA) based on emerging data and exceptional circumstances. The approval process requires close engagement with stakeholders and academia to facilitate appropriate data gathering and enhancing the post - marketing monitoring. The EMA/CHMP have adopted to this process successfully leading global regulatory initiatives, including setting regulatory standards.
as well as setting the norms for pharmacogenomic studies during pharma covigilance evaluation. The presentation will discuss some exemplars and identify some successful approaches while identifying the challenges. Newer initiatives such as adaptive design trials and PRIME initiative \(^6\) are taking shape and being taken up eagerly by several stakeholders. The recent workshop on personalised medicine in collaboration with patient groups is an example of ongoing efforts.

Requirements for rare disease therapies and their development to succeed include the need for understanding of multiple facets including causality, disease prevalence, inheritance patterns and penetrance, and availability of targeted agents including advanced therapy medical products (ATMPs) or gene therapies. The presentation will discuss the potential for development of ATMPs or other therapies using a combined traditional and advanced methodology approach including omics technologies particularly in rare diseases.

UPDATE: Strategies to Alter mRNA Expression that can be Employed in Clinical Trials for Pulmonary Vascular Disease and Right Ventricular Failure

Stefanie Dimmeler

Recent studies suggest that the majority of the human genome is transcribed, but only \(\leq 2\%\) account for protein coding exons. The remaining noncoding sequences include small noncoding RNAs, particularly microRNAs, which are \(\sim 22\) nucleotides in length. MicroRNAs posttranscriptionally control gene expression by targeting multiple mRNAs. By binding to the 3’UTR (untranslated region) of mRNAs, microRNAs induce degradation of the targeted mRNA or they block protein translation. Thereby, one microRNA is able to repress up to hundreds of genes in parallel. In addition to long noncoding RNAs (lncRNAs) with a length of \(>200\) nucleotides comprise a more heterogenic class of noncoding RNAs that include, for example, intergenic lncRNAs, antisense transcripts, and enhancer RNAs. LncRNAs primarily act as epigenetic and transcriptional regulators but may also have additional functions as microRNA sponges or regulators of splicing. Finally, alternative splicing can lead to the formation of circular RNAs, which are highly stable RNAs that may act as microRNA sponges. Among the noncoding RNAs, many of them were described to control the cardiovascular system and may comprise novel therapeutic targets for the treatment of cardiovascular diseases. However, targeting coding RNAs is far more advanced in comparison to noncoding RNAs and has Food and Drug Agency–approved products. The tools to target coding mRNAs include different flavours of antisense oligonucleotides (ASO). Silencing can be achieved by morpholinos or GapmeRs with phosphothioate backbone linkages or silencing RNAs (siRNAs), which are double-stranded RNAs (\(\sim 18–30\) base pairs in length) that are chemically modified, for example, by 2’O-methyl nucleotides to increase stability and limit immunogenicity. Locked nucleic acids (LNAs) are RNA nucleotides with an extra bridge connecting the 2’ oxygen and 4’ carbon in the ribose sugar, which increases the melting temperature and, thereby, augments the efficiency. Most clinical studies used such agents to target genes expressed in liver to either treat liver or metabolic diseases (for review, see Sehgal et al.). For example, siRNA-mediated silencing of PCSK9, an enzyme that regulates cholesterol transport and is highly expressed in liver tissue, was recently reported to efficiently reduce low-density lipoprotein cholesterol and was safely used in a phase I clinical trial. Thus, one may consider using these or other approaches also for targeting the noncoding genome.

Peripheral Balloon Pulmonary Angioplasty in the Treatment of CTEPH: Review of the Clinical Experience

Christoph Wiedenroth

Multiple clinical guidelines recommend pulmonary endarterectomy (PEA) as the therapy of choice in the treatment of chronic thromboembolic pulmonary hypertension (CTEPH) patients. Since 1/3 of all CTEPH patients are not amenable to surgery, treatment alternatives are needed: currently, riociguat, a soluble guanylate cyclase stimulator, is available in many countries as the only approved drug for inoperable CTEPH patients.

Balloon pulmonary angioplasty (BPA) is an evolving interventional approach for selected, inoperable CTEPH patients. Since the first publication of 18 patients in 2001, substantial improvements to the technique have been made. Recently, BPA is performed regularly in various centres worldwide. In addition, hybrid procedures combining PEA with intraoperative BPA for carefully selected patients have been described.

Recent publications from BPA centres reported promising improvements in pulmonary haemodynamics and physical capacity. Complication rates vary inbetween different studies, including vascular injury, bleeding and reperfusion oedema, being the most important. Mortality rates up to 10 % have been described, but may actually be around 2 to 3 %. Until today, there is no standardised BPA technique: patient and target-vessel selection, imaging modality, monitoring and clinical follow-up varies among different centres.

Despite mid-term data are indicating BPA may be a promising therapy for patients with inoperable CTEPH, it is not yet considered an established procedure, because of limited long-term data and a lack of controlled, multicentre trials.

However, data from national and international registries are still outstanding and standardisation of indication, definition of complications and the interventional concepts are needed to generate more evidence.

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**Peripheral Balloon Pulmonary Angioplasty in the Treatment of CTEPH: Review of the Clinical Experience**

Christoph Wiedenroth

Multiple clinical guidelines recommend pulmonary endarterectomy (PEA) as the therapy of choice in the treatment of chronic thromboembolic pulmonary hypertension (CTEPH) patients. Since 1/3 of all CTEPH patients are not amenable to surgery, treatment alternatives are needed: currently, riociguat, a soluble guanylate cyclase stimulator, is available in many countries as the only approved drug for inoperable CTEPH patients.

Balloon pulmonary angioplasty (BPA) is an evolving interventional approach for selected, inoperable CTEPH patients. Since the first publication of 18 patients in 2001, substantial improvements to the technique have been made. Recently, BPA is performed regularly in various centres worldwide. In addition, hybrid procedures combining PEA with intraoperative BPA for carefully selected patients have been described.

Recent publications from BPA centres reported promising improvements in pulmonary haemodynamics and physical capacity. Complication rates vary inbetween different studies, including vascular injury, bleeding and reperfusion oedema, being the most important. Mortality rates up to 10 % have been described, but may actually be around 2 to 3 %. Until today, there is no standardised BPA technique: patient and target-vessel selection, imaging modality, monitoring and clinical follow-up varies among different centres.

Despite mid-term data are indicating BPA may be a promising therapy for patients with inoperable CTEPH, it is not yet considered an established procedure, because of limited long-term data and a lack of controlled, multicentre trials.

However, data from national and international registries are still outstanding and standardisation of indication, definition of complications and the interventional concepts are needed to generate more evidence.
Pulmonary hypertension (PH) is characterised by increased pulmonary vascular resistance (PVR) and mean pulmonary arterial pressure (mPAP) eventually leading to right ventricular dysfunction and without treatment resulting in right heart failure. Over the past decades, various prostanoids with different routes of administration have been approved for the treatment of patients with pulmonary arterial hypertension (PAH). To date, intravenous prostanoids are the treatment of choice for advanced, rapidly progressive, and end-stage PAH. However, the inconvenient route of administration via external, battery driven pumps or catheters and the consequent risk of catheter-associated infections, bloodstream and central-line infections or local side-effects are limiting the use of parenteral prostanoids. Recently, two fully implantable pumps for the delivery of intravenous prostanoids were introduced to overcome these limitations. A US-based study evaluated the SynchroMed® II implantable pump for the delivery of intravenous treprostinil while in Europe the LENUS Pro® pump was recently assessed in a periprocedural safety study and in a prospective observational safety study. Although, the available studies included patients with end-stage disease, the data supports the usage of fully implantable prostanoid infusion pumps as alternative treatment options for patients with PAH. However, implantation, monitoring, filling, and follow-up assessments should be carried out in expert centres.

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