



Ludwig Boltzmann Institute  
Lung Vascular Research

# ANNUAL REPORT



2017

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## Team



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**Director:** Andrea Olschewski/  
Grazyna Kwapiszewska

**Deputy Director:** Grazyna Kwapiszewska/  
Horst Olschewski

**Employee:**

Key Researchers:

Gabor KOVACS  
Grazyna KWAPISZEWSKA  
Leigh MARSH

Scientific Staff':

Alexander AVIAN assoc. MUG  
Valentina BIASIN  
Elisabeth BLANZ assoc. MUG  
Visnja BUBALO  
Slaven CRNKOVIC  
Philipp DOUSCHAN assoc. MUG  
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Bence NAGY  
Lisa OBERREITER (Maternity leave)  
Balazs ODLER  
Horst OLSCHESKI assoc. MUG  
Rita PAPP  
Susanne PFEIFFER  
Michael PIENN  
Sabrina REINISCH (Maternity leave)  
Anita SAHU-OSEN  
Teresa SASSMANN  
Victor SCHEU  
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Helene THEKKEKARA PUTHENPARAMPIL  
Simone TISCHLER assoc. MUG  
(Maternity leave)  
Alexandra Nina TREITLER  
Diana ZABINI

Management:

Claudia JAKOB-PELIKAN  
Stefanie KAINZ (Maternity leave)  
Angelika SCHEIRING

## Partners

We thank our partners, the Ludwig Boltzmann Society, Bayer AG and Medical University of Graz, as well as the Government of Austria for their continuous support.

### **Ludwig Boltzmann Society (<http://www.lbg.ac.at/>)**

The Ludwig Boltzmann Gesellschaft (LBG) is a non-profit organization establishing non-university research institutes in Austria. It is named after the Austrian physicist, mathematician and philosopher Ludwig Boltzmann, whose broad scientific interests still remain the basis for the interdisciplinary of the Ludwig Boltzmann Gesellschaft today. The LBG, which is financed from public and private resources, manages institutes and clusters and currently employs more than 550 people.

### **Medical University of Graz (<http://www.medunigraz.at/>)**

Research activities of the Medical University of Graz (MUG) cover a broad range of clinical as well as pre-clinical fields. The MUG applies a pro-active approach in research management to involve and integrate researchers in international research initiatives. The LBI for Lung Vascular Research fits excellently in this concept and will be an important core for promotion of lung vascular research, diagnostic and innovative therapy of lung vascular diseases at the MUG.

### **Bayer AG (<https://www.bayer.de/>)**

Cardiovascular diseases are in the main focus of Bayer AG (BAG). BAG is currently developing new therapeutic options for the treatment of cardiovascular and lung diseases. The novel treatment for pulmonary hypertension (PH), the soluble guanylate cyclase stimulator Riociguat has recently been launched worldwide for pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH). BAG has a broad experience in pulmonary hypertension associated research and in the transfer of results from “bench to bedside”. The interest of BAG is to further understand the underlying pathophysiology of pulmonary vascular diseases.

## Committees

### Scientific Advisory Board (SAB) – chaired by Prof. Wolfgang Kübler



Prof. Wolfgang Kübler – Charité - Universitätsmedizin Berlin, DE  
<https://physiologie-ccm.charite.de/en/>



Prof. Steve Abman – University of Colorado, US  
[http://www.cudoctors.com/Find\\_A\\_Doctor/Profile/5902](http://www.cudoctors.com/Find_A_Doctor/Profile/5902)



Prof. Nick Morrell – University of Cambridge, UK  
<http://www.med.cam.ac.uk/morrell/>



Prof. Jose Lopez-Barneo – University of Sevilla, ES  
<https://www.ibis-sevilla.es/investigacion/neurociencias/neurobiologia-celular-y-biofisica/lopez-barneo-jose.aspx>



Prof. Dean Sheppard – University of California, US  
<http://profiles.ucsf.edu/dean.sheppard>



**Advisory Board of the Partners (Board) – chaired by Mag. Caroline Schober-Trummler**



Mag. Caroline Schober-Trummler, Medical University of Graz

<http://www.medunigraz.at/rektorat/vizerektorin-fuer-forschung-und-internationales/>



Dr. Peter Mayrhofer, Ludwig Boltzmann Gesellschaft

<http://www.lbg.ac.at/bereichsleitung>



Dr. Heidrun Dorsch, Bayer AG

<http://pharma.bayer.com/>

# 1 The Institute in Overview

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The Ludwig Boltzmann Institute for Lung Vascular Research (LBI-LVR) is a non-profit research institute founded in July 2010 by the Ludwig Boltzmann society (LBG). LBG founded institutes conduct research in the fields of Medicine & Life Sciences or Humanities. The LBI-LVR was established after a demanding two-stage evaluation by international peers who strongly recommended the founding of the institute.

The LBI-LVR, like the other Ludwig Boltzmann Institutes, is established on a partnership between organizations and institutes that traditionally carry out research and organizations that traditionally apply research. The LBI-LVR Consortium currently comprises the Ludwig Boltzmann society as carrier institution in partnership with the Medical University of Graz (MUG) and Bayer AG. The Advisory Board of the LBI-LVR, composed of the representatives of each partner organization (LBG, MUG, and Bayer AG), supervises the progress of the LBI-LVR. The Scientific Advisory Board (SAB) of the LBI-LVR is an independent, world-wide recognized group of experts in pulmonary vascular biology and in pulmonary hypertension and monitors the scientific activities of the institute.

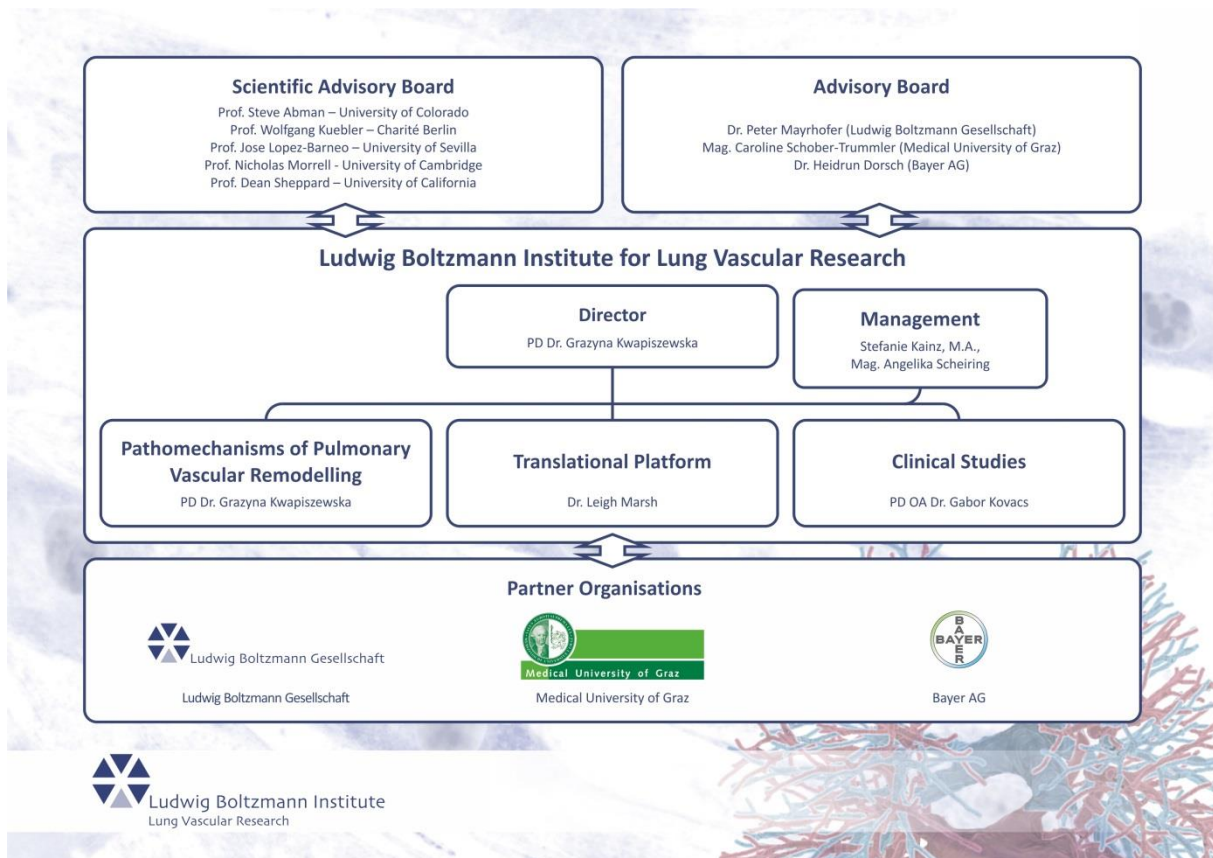
The budget of the institute is approx. 14.9 million Euro cash and in kind for the first seven years. The Ludwig Boltzmann Society covers 56% of the total costs. The remaining 44% of the costs are shared by the consortium of our partners.

The LBI for Lung Vascular Research is predominantly located at the Center for Medical Research (ZMF) at the MUG, which supports the LBI with cutting-edge research facilities guaranteeing high-yield development in this field. The clinical research group is hosted next to the Center for Pulmonary Hypertension of the Division for Pulmonology / Department of Internal Medicine of the MUG.

For contact please visit our website: <http://lvr.lbg.ac.at>



The scheme depicts the structure of our institute



## 1.1 What you should know about Lung Vascular Diseases: Facts, Diagnostics and Therapy

In recent years the area of lung vascular diseases has emerged as a leading field of medical research. The diagnosis and therapy of pulmonary hypertension (PH) has made tremendous progress over the past 20 years. This has continued in 2014, as landmark studies led to the introduction of novel drugs and therapeutic concepts. However, PH remains in many cases a notoriously under-diagnosed chronic and fatal disease. Therefore early recognition of the disease is still crucial. As the diagnosis of PH is performed by invasive right heart catheterisation, the development of reliable non-invasive methods to assess increased pulmonary arterial pressure values may represent an opportunity to promote an early detection. An additional urgent challenge is the presence of PH in heart and chronic lung diseases: large patient populations with severe left heart disease or chronic obstructive lung disease may develop PH during the course of their disease. However, currently no effective treatment options exist for these conditions.

Progressive loss of exercise capacity and worsening dyspnoea represent the most common symptoms of PH. Clinical care for pulmonary vascular diseases is currently extremely costly; therefore, this

condition poses a large burden on the Austrian as well as on the European healthcare system. Current therapies improve exercise capacity and may prolong survival of the affected individuals, but are unfortunately still far away from curing the disease or providing a substantially prolonged lifespan or a good quality of life.

## 1.2 Mission Statement/Aims of the Institute

The LBI-LVR has substantial expertise in the basic mechanisms of pulmonary vasoconstriction and remodelling, combined with a broad and profound clinical background. We aim to provide a significant contribution to early recognition of pulmonary vascular diseases, including pulmonary hypertension, via novel and non-invasive methods and to develop innovative therapeutic strategies for an improved prognosis and better quality of life for the victims of this serious disease. The integrative, multidisciplinary and translational structure of the LBI-LVR allows it to uncover underlying molecular pathways, identify distinct targets for reverse-remodelling therapy, foster drug development based on these targets, and prove these new treatment options in preclinical and clinical proof-of-concept trials.

All our actions, both in research and implementation, will be based on mutual respect and esteem with regard to the patients, our partners, and our staff.

### **The main objectives of the LBI for Lung Vascular Research are:**

- Exploring mechanisms of pulmonary vascular diseases enabling the identification of both novel therapeutic targets and new disease biomarkers that could enable specific diagnosis and therapy monitoring
- Developing new diagnostic tools for non-invasive screening for pulmonary vascular diseases
- Implementing the achieved results into preclinical as well as clinical pilot studies
- Increasing awareness for pulmonary vascular diseases in the society and for healthcare providers



## 1.3 Personal and Human Resources Development

### 1.3.1 Development of the LBI-LVR Staff

The LBI-LVR staff consists of the director, the program line leaders, senior and junior researchers (PhD students) and master students, technicians, study nurses and administrative assistants. Every PhD or postdoctoral fellow has an individual project and each group has scientific independence in generating their individual progress. Please refer to table above for an overview about the staff.

### 1.3.2 Graduations at the LBI-LVR in 2017

In 2017, two colleagues had their defence:

Name	Diploma Theses 2017
NAGY Bence	<p>PhD Thesis: The role of ABCG2 in pulmonary hypertension</p> <p>Final exam on 27 JUN 2017</p> <p>Current status: PostDoc at the LBI LVR</p> 
ODLER Balazs	<p>PhD Thesis: PhD Thesis: Vitamin D and clinical characteristics in asthma-COPD overlap syndrome</p> <p>Final exam on 17 MAY 2017</p> <p>Current status: Landeskrankenhaus Hochsteiermark, Standort Leoben and LBI LVR</p> 

### 1.3.3 Awards and prizes

Name	Awards 2017
CHANDRAN Nagaraj	René Baumgart Research Award 2017, Stuttgart, Germany
CRNKOVIC Slaven	ATS Travel Grant 2017, sponsored by ATS
CRNKOVIC Slaven	ATS International Trainee Travel Award
CRNKOVIC Slaven	3 <sup>rd</sup> Poster Prize in Basic Science, Austrian Society of Pneumology 2017 (ASP)
DOUSCHAN Philipp	Congress Travel Award: European Agency for Studies of the Liver (EASL) 2017
DOUSCHAN Philipp	ATS Travel Grant 2017 by Austrian Society of Pneumology (ASP)
DOUSCHAN Philipp	1 <sup>st</sup> Scientific Poster Prize, Austrian Society of Pneumology (ASP)
DOUSCHAN Philipp	2 <sup>nd</sup> Poster Award, International DACH PH Congress of the German Society of Cardiology
DOUSCHAN Philipp	Abstract Scholarship 2017: American Thoracic Society (ATS)
GUNGL Anna	ATS Travel Grant 2017 by Austrian Society of Pneumology (ASP)
JANDL Katharina	1 <sup>st</sup> Poster Award, PH DACH Symposium Heidelberg, Germany
JANDL Katharina	Land Steiermark Reisekostenzuschuss Stipendium
ODLER Balazs	ERS Travel Grant from Austrian Society of Pneumology (ASP)
TEKKEKARA PUTHENPARAMPIL Helene	1 <sup>st</sup> Poster Prize, Austrian Society of Pneumology (ASP)
TEKKEKARA PUTHENPARAMPIL Helene	Short Time Fellowship, Austrian Society of Pneumology (ASP)
ZABINI Diana	1 <sup>st</sup> Poster Prize PH-DACH Symposium

### 1.3.4 Conferences and Meetings of the LBI-LVR Staff

Valentina Biasin: 19th International Vascular Biology Meeting. Boston, USA; March 2017

Valentina Biasin: Grover Conference; September 6-10/2017 Lost Valley Conference Center, Sedalia, CO

Slaven Crnkovic: ATS conference 2017, Washington DC, USA, May 2017

Slaven Crnkovic: ÖGP Congress, October 6-7, 2017

Philipp Douschan: Austrian Society of Pneumology (ASP) 2017; Innsbruck, Austria

Philipp Douschan: European Agency for Studies of the Liver (EASL) 2017; Amsterdam, Netherlands

Philipp Douschan: European Respiratory Society (ERS) 2017; Milan, Italy

Nicola Giuliani: ÖGP Congress 2017, Innsbruck, Austria

Anna Gungl: ATS conference 2017, Washington DC, USA, May 2017

Katharina Jandl: ATS conference 2017, Washington DC, USA, May 2017

Katharina Jandl: FEBS Advanced Lecture Course- Matrix Pathobiology, Spetses, Greece, June 2017

Katharina Jandl: PH-DACH Herbs Symposium, Heidelberg, Germany; November 2017

Grazyna Kwapiszewska: PH Patiententreffen, Graz, AUSTRIA

Grazyna Kwapiszewska: ATS conference 2017, Washington DC, USA, May 2017

Leigh Marsh: ATS conference 2017, Washington DC, USA, May 2017

Michael Pienn: ÖGP Congress 2017, Innsbruck, Austria

Helena Thekkekara Puthenparampil: PH. ÖGP Congress, October 6-7, 2017

Diana Zabini: ÖGP Congress, October 6-7, 2017

Diana Zabini: PH – DACH Herbstsymposium, October 26-28 2017; Heidelberg, GERMANY

### 1.3.5 Patents of the LBI-LVR

Patents	Inventors
Biomarker for the diagnosis of pulmonary hypertension (PH) Patent File No. 16159415.5	H. Olschewski (LBI-LVR), A. Olschewski (LBI-LVR), CH. Magnes (Joanneum Research), N. Bordag, S. Narath (CBmed GmbH), E. Gander (Joanneum Research) and B. Nagy (LBI-LVR)
Method for non-invasive diagnosis of pulmonary hypertension using impedance cardiography Patent File No. is A 50719/2016.	M. Pienn (LBI-LVR), H. Olschewski (LBI-LVR), G. Kovacs (LBI-LVR) and Z. Bálint (LBI-LVR)
Method and Device for Processing Impedance Cardiograms for the Determination of a Presence of Pulmonary Hypertension in a Patient and Impedance Cardiograph with such a Device Patent Nr. 518396; Austrian Patent Office, Vienna, Austria; October 15th, 2017	M. Pienn (LBI-LVR), H. Olschewski (LBI-LVR), G. Kovacs G., Z. Bálint.(LBI-LVR)

## 1.4 Highlights 2017

### Completion of Evaluation of the LBI 2016/2017

After six and a half years, the work of the LBI was assessed by an international committee on the 7<sup>th</sup> and 8<sup>th</sup> of November, 2016. Within the framework of the evaluation, the Institute's scientific projects and their results were presented by the LBI staff and were thoroughly discussed with the evaluators. The evaluation was guided by Prof. **Lewis Rubin**, who has been working in the field of pulmonary hypertension since the early 1990s and has participated in almost all important studies in this context. He is one of the most famous and respected researchers in his field. The other members of the evaluation committee are also highly recognized researchers and experts in their respective fields. In 2017 our institute has received positive evaluation with the recommendation to be prolonged for the next period. We would like to give the gratitude to the evaluation team for their time and constructive comments, bringing our institute forward!

The Revaluators at a glance:

**Prof. Lucie Clapp**, University College London

**Prof. Lewis J. Rubin**, University of California

**Prof. Jason X.-J. Yuan**, University of Arizona

**Dr. Christine Petry**, Deutsche Forschungsgemeinschaft





## American Thoracic Society (ATS) 2017

LBI-LVR had a significant presence at the annual meeting of the American Thoracic Society held in Washington, DC, May 19-24, 2017. At the world's largest gathering for respiratory biology and medicine both our senior and young researchers were selected to give notable talks and oral presentations. **Andrea Olschewski** participated in a pro-and-con debate about the role of inflammation in pulmonary hypertension. **Gabor Kovacs** took part in PAH-ICON consortium discussing the next steps in genomic analysis. **Grazyna Kwapiszewska** was in the steering committee of the pulmonary circulation subgroup. **Anna Gungl**, **Slaven Crnkovic** and **Philipp Douschan** gave oral presentations of their research work.

The impact and the quality of research was additionally recognised as **Slaven Crnkovic** was awarded an ATS International Trainee Travel Scholarship, while **Philipp Douschan** received an ATS Abstract Award.



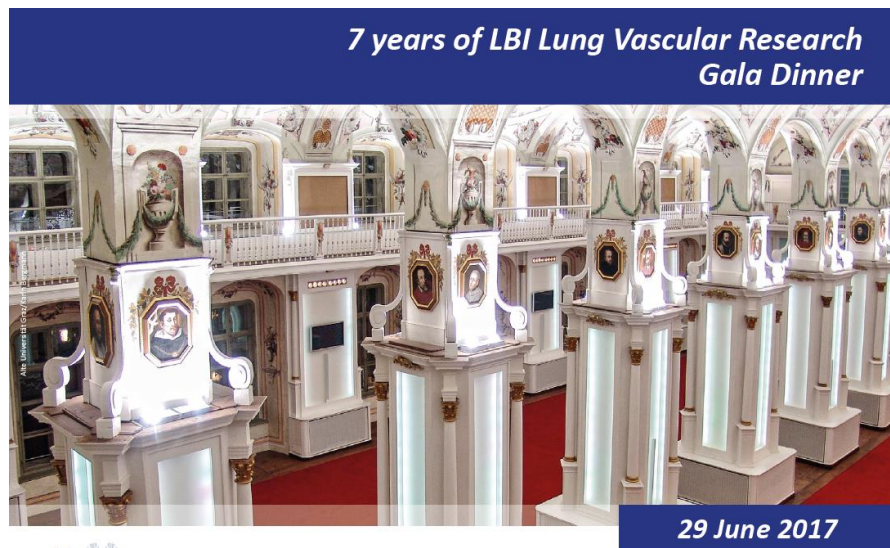
Anna Gungl and Philipp Douschan meet the President of the ASP Prim. Univ.-Prof. Dr. Meinhard Kneussl.



LBI LVR members celebrating the successful ATS meeting.



## Seven Years Anniversary of LBI LVR



On June 29<sup>th</sup> the LBI LVR celebrated its 7<sup>th</sup> anniversary and at the same time celebrated the renewal for further 7 years at the “Alte Uni” in Graz. It was a great party with many wishers and High-profile guests.

Prof. **Andrea Olschewski** as the Director of the Institute opened the

celebration, followed by notable guests including Mag. **Claudia Lingner**, Managing Director LBG, Mag. **Caroline Schober-Trummler**, Vice-Rector for Research and International Matters of Medical University of Graz, Dr. **Heidrun Dorsch** Alliance Manager Bayer AG, Prim. **Meinhard Kneussl**, President Österreichische Gesellschaft für Pneumologie and Prof. **Ardeschir Ghofrani**, Justus Liebig University in Giessen.



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## Vascular Research Symposium



On June 30<sup>th</sup> the Institute organized the Vascular Viewpoint Symposium at the Universalmuseum Joanneum. We hosted several outstanding experts in the field of chronic lung diseases to discuss with them the importance of vasculature in the lung diseases.

**Jürgen Behr**, Ludwig Maximilian University in Germany

“Pulmonary Vasculopathy in Chronic Lung Disease”



**Martin Kolb**, McMaster University in Canada

“Blood Vessels in IPF – Bystander or Driver of the Disease”



**Joan Albert Barbera**, Hospital Clinic Barcelona in Spain

“Endothelial Dysfunction in COPD”





**Edwin K. Silverman**, Harvard Medical School in USA

"How Genomics Can Help us to Understand the Associations between the Vascular System and COPD"

**Paul Hassoun**, Johns Hopkins University in USA

"Right Ventricular-Pulmonary Vascular Coupling in Scleroderma-Associated PAH: Solving a Conundrum"



### Andrea Olschewski new Vice-Rector for Medicine at Johannes Kepler University Linz



**Andrea Olschewski**, Director of the Ludwig Boltzmann Institute for Lung Vascular Research, Graz, took up a new assignment as Vice-Rector for Medicine at the Johannes Kepler University of Linz. We wish her all the best for the new job and would like to thank her for her strength, her commitment and her versatility in building this institute for lung vascular research.

### Grazyna Kwapiszewska new Director of the LBI-LVR

In November 14th, 2017 **Grazyna Kwapiszewska** took over the management of the LBI-LVR. The molecular biologist has been working at the institute since 2011 as the head of the research group Pathomechanisms of pulmonary vascular remodelling and serving as the deputy director. Grazyna Kwapiszewska studied molecular biology and biotechnology at the Adam Mickiewicz University in Poznań (Poland) and received her doctorate summa cum laude at the Justus Liebig University in Gießen (Germany). In 2015 she habilitated in the field of molecular pathology at the Medical University of Graz. She is a reviewer in several international journals and editorial boards of professional journals such as the American Journal of Respiratory Cell and Molecular Biology.



### Horst Olschewski new Deputy Director of LBI-LVR



**Horst Olschewski** is the new Deputy Director of the LBI-LVR. As the Chair of the Division of Pulmonology, MUG/LKH Graz he will contribute his expertise and his clinical and scientific knowledge about pulmonary diseases to our Institute. Horst Olschewski studied human medicine at the Justus Liebig University in Gießen (Germany) and in 2000 he habilitated in the field of pulmonology. Since 2005 he is a Full Professor and Director of the Division of Pulmonology, Department of Internal Medicine, Medical University of Graz, Austria. He is chairman of the Working-group Pulmonary Circulation of the Austrian Society of Pneumology ASP and AG25 of German Cardiologic Society and co-organized some conferences.

### Symposium of the Austrian Society of Pneumology (ÖGP 2017): 6 awards of our institute!

The Annual Meeting of the Austrian Society of Pneumology, which took place from the 5<sup>th</sup> till the 7<sup>th</sup> of October 2017 in Innsbruck, was a very successful event for our institute. Three of our employees were honoured with scientific prizes for basic and clinical research at the Congress. Additionally three travel awards went to our institute. We congratulate our colleagues!

- THEKKEKARA-PUTHENPARAMPIL Helene (LBI for Lung Vascular Research, basic research):  
1<sup>st</sup> Poster Prize
- CRNKOVIC Slaven (LBI for Lung Vascular Research, basic research): 3<sup>rd</sup> Poster Prize
- DOUSCHAN Philipp (Div. Pulmonology, UKIM and LBI for Lung Vascular Research, clinical research): 1<sup>st</sup> Poster Prize
- DOUSCHAN Philipp: ATS Travel Grant 2017
- ODLER Balazs: ERS Travel Grant
- THEKKEKARA-PUTHENPARAMPIL Helene: Short Time Fellowship 2017





## 1.5 Public Relations

### Science Lunch “Under pressure” May 9<sup>th</sup>, 2017

The Science Lunch “Under pressure” took place on May 9<sup>th</sup>, 2017 in the Lecture Hall of the Medical University of Graz. The meeting was organized by the PH Austria Initiative Pulmonary Hypertension. President **Gerry Fischer** welcomed the audience in the full Lecture Hall. Horst Olschewski informed about „Pulmonary Hypertension– diagnosis of a rare disease with high mortality“. He talked in his lecture about the latest questions in Diagnostics in Pulmonary Hypertension.

**Vasile Foris** presented the latest information about „Biomarkers for Pulmonary Hypertension“. Biomarkers (special Laboratory parameters) play a more and more important role in the field of Medicine.

**Eva Otter** and **Gerry Fischer** then gave an update about their activities in the PH Austria Initiative. The interested participants had the opportunity to get in touch with the latest scientific information on Pulmonary Hypertension.



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## Patient meeting on September 7th, 2017

This year the PH patient meeting took place with 50 participants in the Austria Trend Hotel Graz. **Eva Otter** from PH Austria Initiative Lungenhochdruck welcomed the participants and gave an overview of the activity of their Initiative. Afterwards **Horst Olschewski**, **Gabor Kovacs** and **Grazyna Kwapiszewska** presented overviews about the supportive therapies of pulmonary hypertension, the various drugs that have been available for pulmonary hypertension since the mid-1990s and the major mechanisms of lung vascular remodelling which is dependent on the form of pulmonary hypertension. After the official part, the patient's meeting ended with a get-together, where everybody had the possibility to exchange experiences.



## Newsletter

In addition, the Newsletter of the Pulmo-Outpatient Clinic of the Hospital Graz and the Ludwig Boltzmann Institute for Lung Vascular Research for patients with pulmonary hypertension or a high risk for this disease is available via email by Daniela Kleinschek: [daniela.kleinschek@lvr.lbg.ac.at](mailto:daniela.kleinschek@lvr.lbg.ac.at) or online at the LBI LVR Homepage.



Last but not least, our LBI for Lung Vascular Research has received several invitations to present the research work and aims of the institute to the broad public. A list of the press appearances in 2017 is given here:

- „Die Suche nach Warnsignalen für Krebs“, [derstandard.at](http://derstandard.at) am 03.04.2017
- „Forschungspreis: Chandran Nagaraj“, [medunigraz.at](http://medunigraz.at) am 08.05.2017
- „Die ÖGP fördert den wissenschaftlichen Nachwuchs in Österreich“, [ogp.at](http://ogp.at) am 08.08.2017
- „Experten warnen: Unerkannter Lungenhochdruck kann lebensgefährlich sein!“, [ogp.at](http://ogp.at) am 06.10.2017

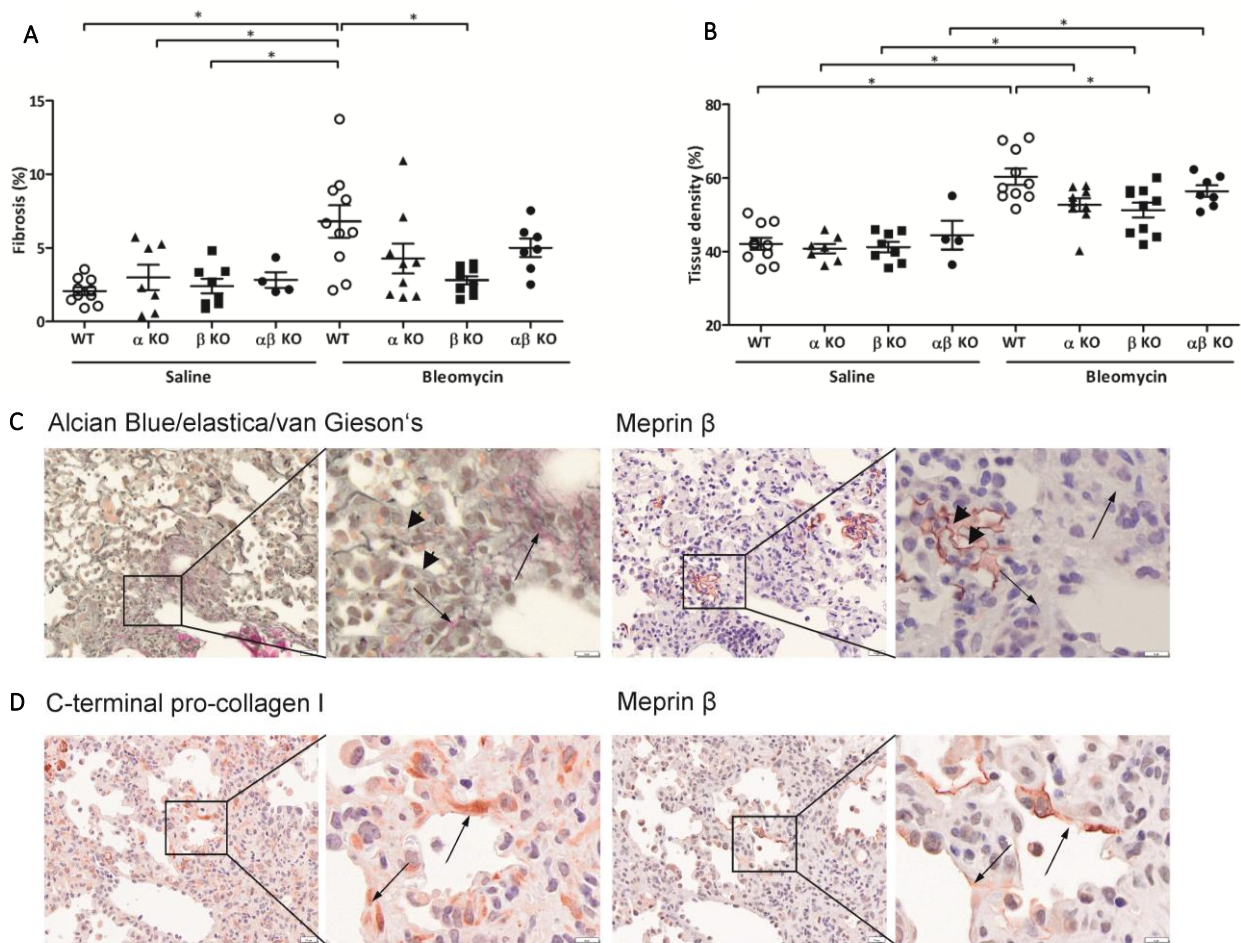
## 2 Research Program 2017

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### 2.1 Pathomechanisms of Pulmonary Vascular Remodelling



The main goal of this program line is to understand the mechanisms underlying vascular remodelling in the diverse forms of pulmonary hypertension. For example we have previously shown that Fra-2 overexpressing mice, which are characterized by vascular remodelling and parenchymal fibrosis, expressed higher levels of metalloprotease meprin  $\beta$  (Biasin et al. J Pathol 2014). As meprin  $\beta$  have been shown to enhance collagen maturation and collagen production and deposition is a hallmark of lung fibrosis, we have now investigated the role of meprin  $\beta$  in fibrotic lung disease. Indeed, in the lung of bleomycin treated meprin  $\beta$  knock out mice we have observed lower collagen content. In bleomycin-treated lungs, meprin  $\beta$  was adjacent to immature collagen and pro-collagen I, while weak presence or absence of meprin  $\beta$  was observed in regions with mature collagen. Our results suggest an important role of meprin  $\beta$  in the in vivo process of collagen maturation, which take place in fibrotic lung disease. These findings were specific for meprin  $\beta$ , as these changes were observed neither in meprin  $\alpha$  nor meprin  $\alpha\beta$  knock out mice.

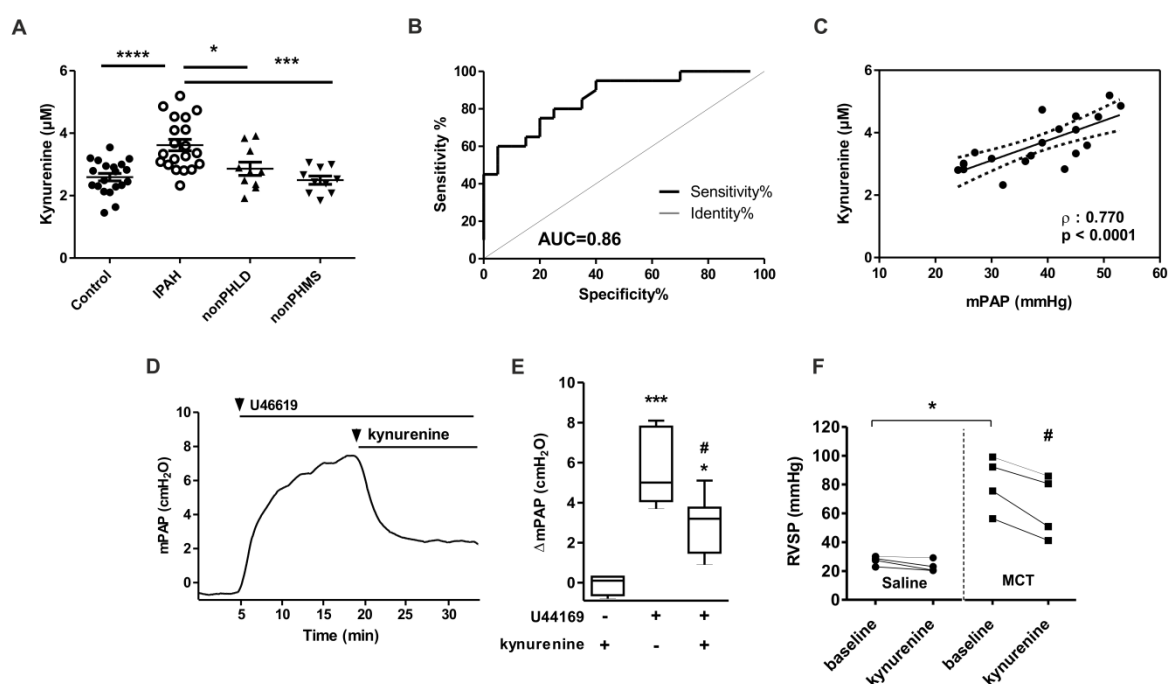


**Figure 1: Meprin  $\beta$  contributes to collagen maturation in lung fibrosis.** Quantification of a) fibrosis and b) tissue density from Masson's trichrome staining slides of meprin  $\alpha$ , meprin  $\beta$ , meprin  $\alpha\beta$  KO and wt littermate mice after 14 days saline or bleomycin treatment (\* $p < 0.05$ ). c) Alcian blue/elastica/van Gieson's staining and meprin  $\beta$  in serial slides from lung wt mice after 14 days bleomycin treatment. Arrows point at mature collagen (pink) while arrowheads point at immature collagen (greenish grey). Scale bars show 50  $\mu$ m in the overview picture and 10  $\mu$ m in the zoomed area. d) Representative pictures of immunohistochemical staining in serial slides for C-terminal-pro-collagen I and meprin  $\beta$ . Arrows point at co-localization of meprin  $\beta$  and C-terminal pro-collagen I. Scale bars show 50  $\mu$ m in the overview picture and 10  $\mu$ m in the zoomed area. Modified from Biasin et al. Sci Rep. 2017

The pulmonary circulation is normally a low pressure and low resistance system. The pulmonary vascular tone can exhibit a balance in maintaining substantial contractile and relaxing responses. Previously we have shown the increased pulmonary vascular resistance in pathological conditions could be modulated with various exogenous agents (Li Y et al. Am J Respir Cell Mol Biol. 2012, Tang B et al. Am J Respir Cell Mol Biol. 2009, Nagaraj C et al. Eur Respir J. 2013, Nagaraj C et al. Eur Respir J. 2016). Here we have investigated role of an endogenous metabolite kynurenine and p22phox dependent NADPH oxidase in regulating pulmonary vascular tone in pathological and physiological condition.

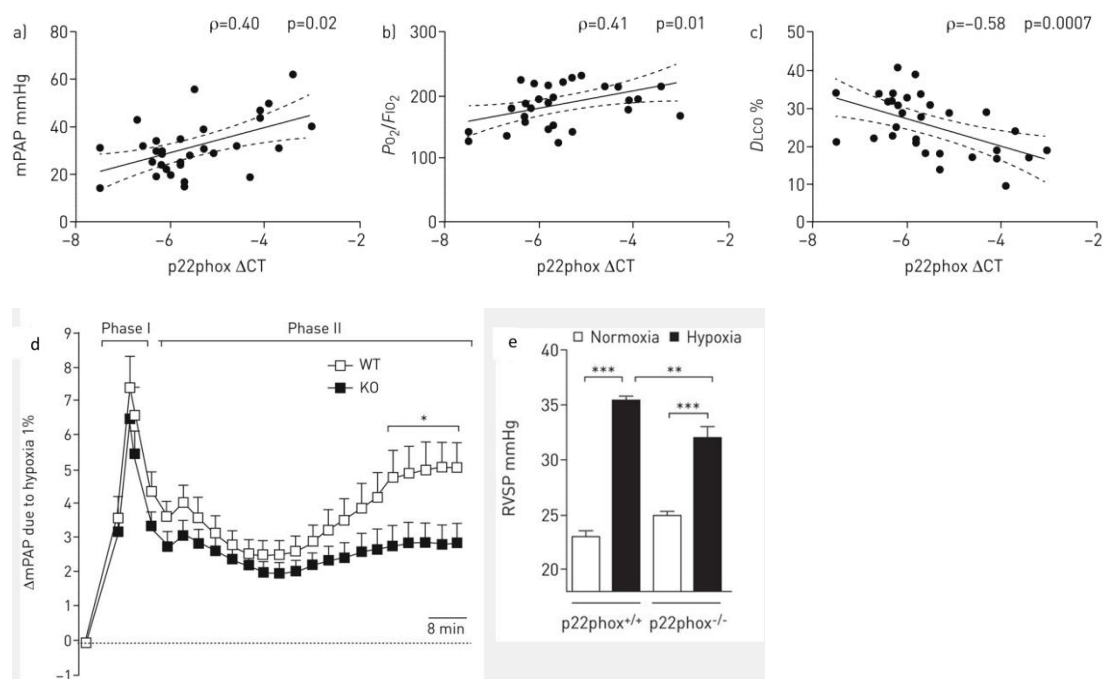


The tryptophan metabolite kynurenine is significantly increased in pulmonary arterial hypertension (PAH) patients, and it is a potent vasodilator of systemic arteries, however it is not known what is its role in IPAH. Our study revealed that the circulating level of kynurenine is increased in IPAH patients compared to healthy controls or non-pulmonary hypertensive patients. Kynurenine displayed very strong correlation with mPAP values and it was able to distinguish IPAH patients from non-IPAH patients with a high sensitivity and specificity. The vasoactive role of kynurenine was investigated ex vivo in isolated perfused mouse lungs and in vivo in the monocrotaline rat model of pulmonary hypertension (PH). In both cases, kynurenine was able to induce significant vasodilation. These results suggest kynurenine as a new biomarker and a new therapeutic option for PH.



**Figure 2: The importance of kynurenine in pulmonary hypertension** A) Serum concentration of kynurenine in control group (n=20), IPAH patients (n=20), non-PH chronic lung disease patients (n=10) and non-PH metabolic syndrome patients (n=10). B) Receiver-operating characteristic (ROC) curves for kynurenine determining  $mPAP \geq 25$  mmHg (AUC: area under the curve). C) Serum kynurenine correlation with mPAP (mean pulmonary arterial pressure). (D) Representative mean pulmonary arterial pressure tracing in the presence of U46619 and kynurenine in the isolated-perfused and ventilated mouse lung model. (E) Boxes and whiskers (Min to Max) represent the relative changes in mPAP in response to kynurenine (3mM), in non-pre-constricted (n=4) and pre-constricted mouse lungs (U44169, n=6) measured by IPL (# corresponds to significant difference from pre-constricted lungs). Subset (F) shows RVSP before (baseline) and after single bolus of kynurenine in saline and MCT-treated rats ( $p < 0.05$  and  $p < 0.01$ ). Modified from Nagy et al. Am J Physiol Lung Cell Mol Physiol. 2017

Hypoxic pulmonary vasoconstriction (HPV) can be defined as a rapid, reversible increase in pulmonary vascular resistance caused by contraction of the small muscular pulmonary in response to physiological levels of hypoxia. As K<sup>+</sup> channels are the effector of the hypoxic signal, in this study we investigated the crucial role of p22phox; a regulatory subunit of NADPH oxidases, in HPV, vascular remodelling and COPD associated pulmonary hypertension. By comparing control lungs to diseased COPD lungs, we show a significant reduction in p22phox expression in the COPD lungs. Interestingly the lowest p22phox expression was found in patients with a relatively preserved diffusing capacity of the lung for carbon monoxide (DLCO), higher p22phox expression was associated with a better oxygenation index, a lower DLCO and the presence of pulmonary hypertension. In p22phox knock-out mice, HPV was significantly impaired by its action only on phase II with preserved phase I and in the chronic hypoxic setting; lack of p22phox was associated with decreased pulmonary vascular remodelling and improved right ventricular function. These results suggest that a loss of p22phox might result in poor oxygenation in COPD patients due to impaired HPV and ventilation perfusion mismatch.



**Figure 3: Correlation of p22phox levels with clinical parameters of chronic obstructive pulmonary disease (COPD) patients who underwent lung transplantation.** p22phox correlation with a) mean pulmonary artery pressure (mPAP); b) oxygenation ratio (oxygen tension ( $PO_2$ )/inspiratory oxygen fraction ( $FIO_2$ )); and c) diffusing capacity of the lung for carbon monoxide (DLCO), the clinical indicator of lung parenchymal damage. d) HPV response, determined as  $\Delta$ mPAP, indicate reduced sustained HPV in p22phox<sup>-/-</sup> mice. e) Data showing the results obtained after 5 weeks of hypoxic treatment (10% oxygen) of p22phox<sup>+/+</sup> and p22phox<sup>-/-</sup> mice. Right ventricular systolic pressure (RVSP). Modified from Nagaraj C et al. Eur Respir J. 2017

## Scientific Cooperations

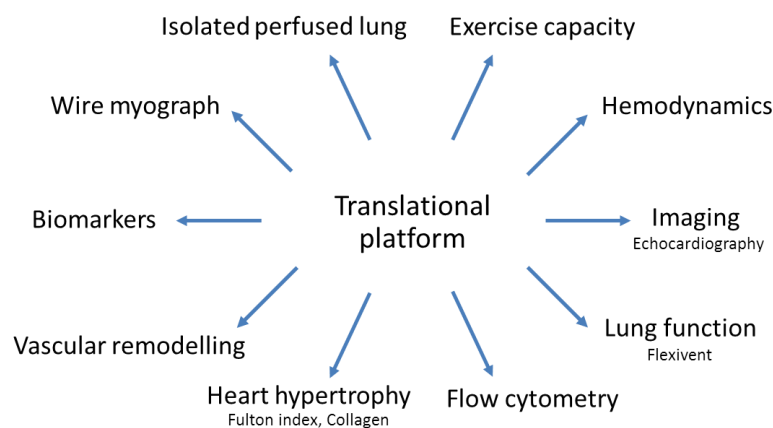
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WILHELM Jochen Dr., University Giessen Lung Centre, Giessen, Germany  
WITZENRATH Martin Prof., Charité –University Medical Department, Berlin, Germany  
WYGRECKA Malgorzata Prof., University Giessen Lung Centre, Giessen, Germany



## 2.2 Translation Platform of the LBI-LVR



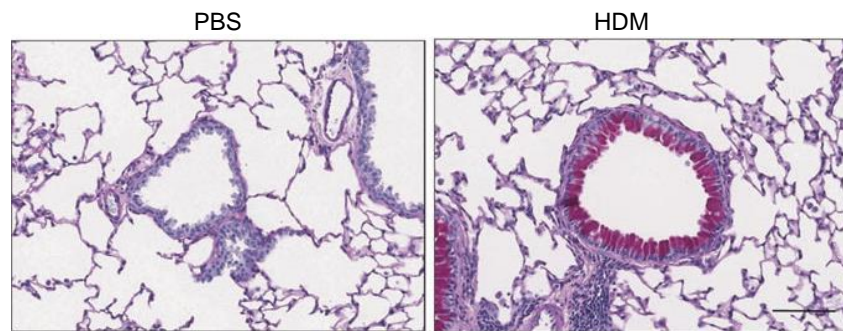
The Translational Platform unites the institute's molecular and clinical arms. The use of pre-clinical models permits the investigation of specific genes or molecules in vivo and how they contribute to disease pathogenesis. Here the Translation platform provides crucial resources facilitating the planning, coordination and experimental implementation. All experiments and analyses are performed according to established standard operating procedures. An overview of available techniques and readouts are shown in Figure 1.



**Figure 1. Overview of techniques available in the translation platform**

How several of these techniques have been implemented can be observed in our publication detailing how increased expression of the important NADPH oxidase adapter molecule, p22phox mediates airway hyperresponsiveness. In our study by Nagaraj et al. we identified increased expression of p22phox in lungs of asthmatic patients and in an experimental model. The induced airway hyperresponsiveness and mucus hypersecretion (Figure 2) are a result of increased oxidative stress/ROS from the p22phox-dependent NADPH oxidase, which in turn activates the downstream STAT6 signalling molecule to control several pathological features of asthma. This study indicates that

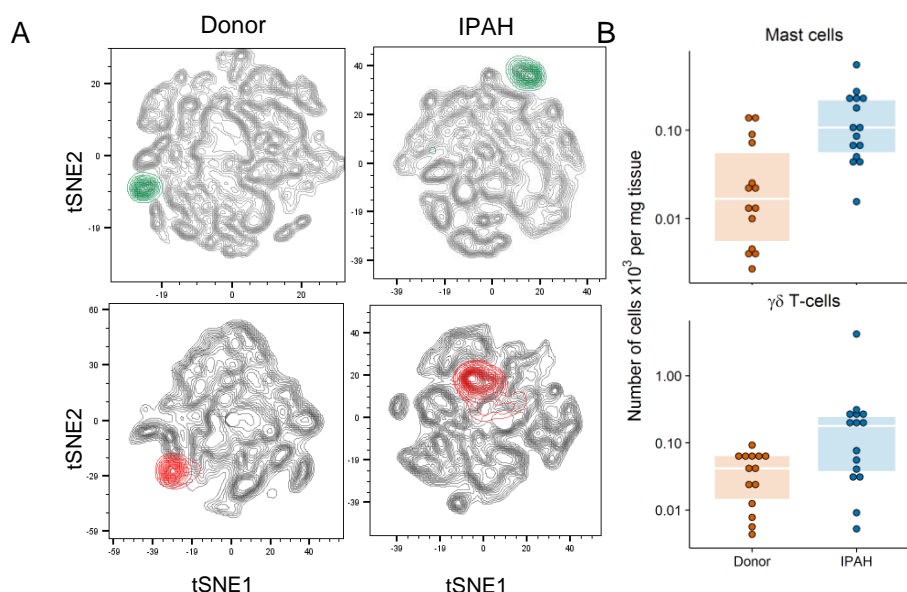
selective interference of p22phox could be therapeutically relevant for the management of clinical asthma.



**Figure 2. Exposure to house mite extract induces goblet cell hyperplasia and mucus production as determined Periodic Acid Schiff-haematoxylin staining.** Scale bar indicates 100  $\mu$ m.

In our recent publication “The inflammatory cell landscape in the lungs of patients with idiopathic pulmonary arterial hypertension” by Marsh et al., ERJ 2018, we utilised a novel unbiased computational flow cytometry approach to simultaneously evaluate the presence and abundance of 21 different inflammatory cell populations in patients with idiopathic pulmonary arterial hypertension in comparison to controls. By applying several bioinformatic and traditional statistical approaches we were able to discriminate two groups and highlight not only changes in cell distribution but also an increased abundance of inflammatory cells in the lungs of IPAH patients.

Two example populations, 1) mast cells (previously shown to be regulated in pulmonary hypertension, and 2)  $\gamma\delta$ T-cells (novel and identified in our study) that were differentially abundant in IPAH lungs are shown in Figure 3.



**FIGURE 3. T-stochastic neighbour embedding (t-SNE) visualisation of two regulated cell populations in IPAH.** A) t-SNE composite dimension plots of down-sampled and concatenated CD45+ cells derived from flow cytometric data with overlaid manually gated cell (Mast cells – green;  $\gamma\delta$ T-cells – red) populations. B) Example cell populations differentially abundant between IPAH and donor lungs as identified by flow cytometry. Boxplots show median and interquartile range. Adapted from Marsh et al. ERJ 2018

### Research cooperations

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## 2.3 Clinical Studies

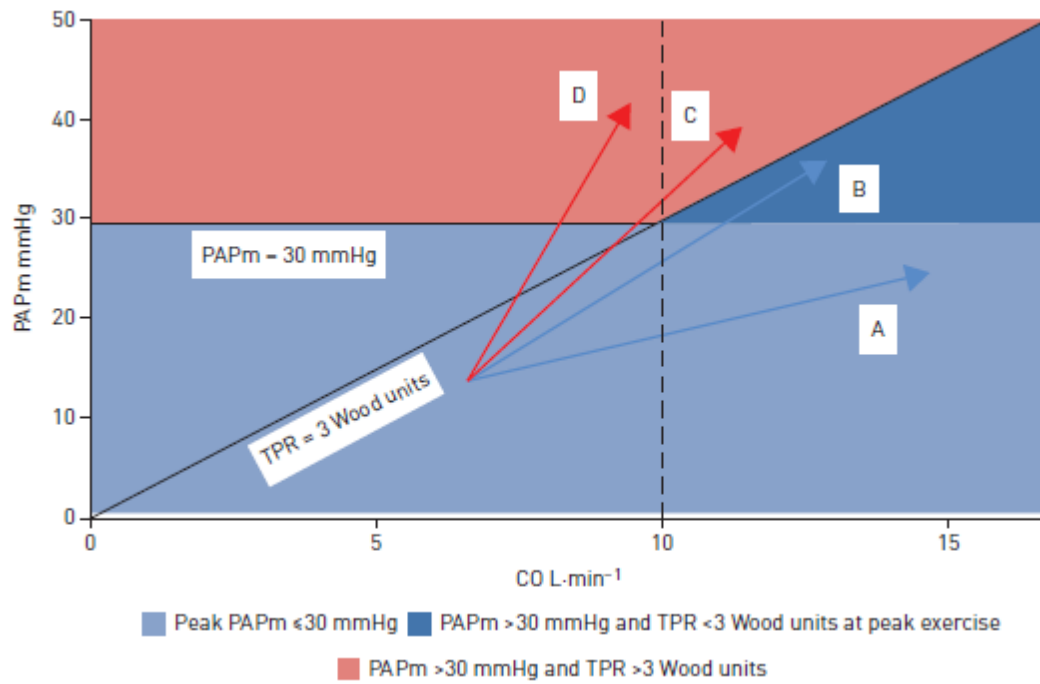


### Project overview and main research results

The major research interest of the clinical program line of the LBI is the promotion of early diagnosis of pulmonary hypertension (PH), the appropriate integration of innovative non-invasive tools in the management of PH, the understanding of the clinical relevance of pulmonary hemodynamics during exercise and the recognition of a pulmonary vascular component in chronic lung diseases.

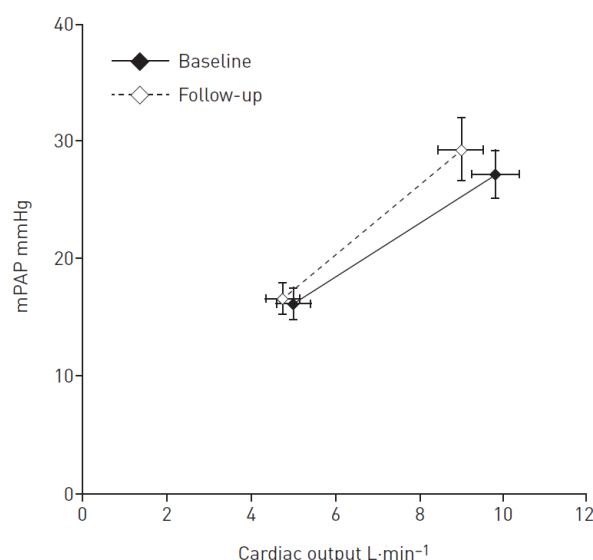
### Pulmonary hemodynamics during exercise

In 2017, the major results of the ERS Task Force on pulmonary hemodynamics during exercise were presented at the annual conference of the European Respiratory Society and published in the European Respiratory Journal. Our program line gave the first and the corresponding author of the group. According to this expert statement, the term “exercise pulmonary hypertension” (exercise PH) may be most adequate to describe an abnormal pulmonary hemodynamic response characterized by an excessive pulmonary arterial pressure (PAP) increase in relation to flow during exercise. Exercise PH may be best defined as the presence of resting mean PAP < 25mmHg and mean PAP surpassing 30mmHg during exercise with total pulmonary resistance > 3WU (see Figure). Exercise PH represents the hemodynamic appearance of early pulmonary vascular disease, left heart disease, lung disease or a combination of these conditions. Exercise PH is associated with the presence of a modest elevation of resting mean PAP and requires clinical follow-up, particularly if risk factors for PH are present.



**Figure 1: Definition of exercise pulmonary hypertension according to the task force proposal.** The definition is based on the relationship between mean pulmonary arterial pressure (PAPm) and cardiac output (CO) at peak exercise by HERVE et al. ERJ 2015. The light blue area represents peak PAPm values  $\leq$  30 mmHg (normal range according to previous exercise pulmonary hypertension definition). The dark blue triangle represents PAPm values > 30 mmHg, but total pulmonary resistance (TPR) < 3 Wood units at peak exercise. Reaching this area was considered pathological according to the previous definition of exercise pulmonary hypertension, but normal based on the proposal of this task force. The red area represents values with PAPm > 30 mmHg and TPR > 3 Wood units corresponding to exercise pulmonary hypertension proposed by the task force. Line A represents a patient with a mild increase of PAPm and normal pulmonary haemodynamics during exercise. Line B represents a patient with a steeper PAPm/CO ratio and PAPm > 30 mmHg, but TPR < 3 Wood units during exercise. In this case, the criteria of the proposed definition of exercise pulmonary hypertension are not fulfilled. Lines C and D represent patients with PAPm > 30 mmHg and TPR > 3 Wood units at peak exercise and thus fulfilling the proposed criteria of exercise pulmonary hypertension (Kovacs et al. ERJ 2017)

In addition, a follow-up study was published in 2017, analyzing the changes in pulmonary hemodynamics during exercise in scleroderma patients without PAH. We found that over a 4-year follow-up period, patients developed a mild but significant deterioration of pulmonary hemodynamics during exercise and of exercise capacity, indicating a progression of pulmonary vascular disease. The manifestation rate of RHC-confirmed PAH was 0.75 cases per 100 patient-years.



**Figure 2. Increase in mean pulmonary arterial pressure (mPAP; cardiac output slope assessed between rest and 50 W) at incremental cardiac output values during exercise.** Comparison between baseline and follow-up right heart catheterisation in n=28 patients. (Kovacs et al. ERJ 2017)

In collaboration with further research groups, we assessed the diagnostic accuracy of key parameters derived from cardiopulmonary exercise testing (CPET) for detecting and ruling out systemic sclerosis-associated pulmonary arterial hypertension (PAH) in a multicenter setting. We found that peak oxygen uptake (peak VO<sub>2</sub>) showed highest diagnostic accuracy (sensitivity 87.5%, specificity 74.8% at a threshold level of 13.8 mL/min/kg). A peakVO<sub>2</sub> of >18.7 mL/kg/min excluded PAH in our cohort (negative predictive value 1.0). A nadir VE/VCO<sub>2</sub> ratio of >45.5 showed a positive predictive value of 1.0. Therefore, CPET appeared to be a safe and valuable method in the non-invasive detection of systemic sclerosis-associated PAH. It may be particularly beneficial for reducing unnecessary right heart catheterization procedures.

### Non-invasive tools in the management of PH

In 2017, our previously initiated studies focusing on cardiac MRI and chest CT were continued. We validated formulas from the literature calculating mean pulmonary arterial pressure (PAP) and pulmonary vascular resistance (PVR) from cardiac MRI-derived measures in our prospective cohort of almost 200 PH patients and patients at risk of PH. We found significant correlations, according to the literature formula, with r values ranging from 0.43 to 0.72 for PAP and 0.26 to 0.75 for PVR. The best

correlations were found using the multi-parametric models ( $r=0.72$ , and  $r=0.75$ , for PAP and PVR, respectively) based on the following formulas:  $PAPMR = \text{Areamin}/RVEF$  (Moral, S. et al. *Int J Cardiol* 2012;161:25-30) and  $PVRMR = 19.38 - (4.62 \times \ln(\text{velocitymean, average})) - (0.08 \times RVEF)$  (García-Alvarez, A. et al. *Eur Heart J* 2011;32:2438-45). The correlations found in the original cohorts were  $r=0.61$  and  $r=0.84$ , respectively. We also evaluated how right ventricular cardiac output as assessed by MRI correlates with invasively assessed cardiac output and if MRI right ventricular and pulmonary arterial flow readouts are associated with exercise capacity. We found that right ventricular function as assessed by cardiac output determined by MRI and right heart catheterization were strongly correlated ( $p<0.0005$ ,  $r=0.71$ ). Right ventricular functional parameters generally showed moderate correlations with exercise capacity (six minute walk distance, peak VO<sub>2</sub>). Among the MRI derived right ventricular volumetric parameters, right ventricular ejection fraction showed the best correlation with the six minute walk distance ( $p<0.0005$ ,  $r=0.38$ ) and right ventricular end-systolic volume index with peak VO<sub>2</sub> ( $p<0.05$ ,  $r=0.32$ ). Among the MRI derived pulmonary flow parameters, pulmonary peak velocity showed the best correlation with the six minute walk distance ( $p<0.005$ ,  $r=0.33$ ) and pulmonary net forward volume with peak VO<sub>2</sub> ( $p<0.005$ ,  $r=0.45$ ).

In order to determine morphologic readouts from a large number of healthy subjects, we analyzed computed tomography pulmonary angiography datasets, negative for pulmonary embolism, and other thoracic pathologies, using a fully-automatic, in-house developed artery/vein separation algorithm. The number, volume, and tortuosity of the vessels in a diameter range between 2 and 10mm were determined in over 100 subjects. Our fully-automatic artery/vein separation algorithm provided reliable measures of pulmonary arteries and veins with respect to age and gender. There was a large variation between subjects in all readouts. No relevant dependence on age, gender, or vessel type was observed. These data may provide reference values for morphometric analysis of lung vessels. In addition, we analyzed dynamic CT images of over 50 patients undergoing right heart catheterization in a prospective manner with the question, if the presence of PH can be predicted based on the propagation time of contrast medium in the pulmonary arteries. Results are expected in 2018.

Novel biomarkers may play an important role in the non-invasive clinical management of PH. Our aim was to investigate the role of the tryptophan metabolite kynurenine in the pulmonary circulation. In idiopathic PAH vs. control serum, kynurenine was significantly elevated, and strongly associated with PH (area under the curve = 0.86), but kynurenine levels were not elevated in lung disease and metabolic syndrome. Among all investigated tryptophan metabolites, kynurenine displayed the strongest correlation with mean pulmonary arterial pressure (mPAP) ( $\rho: 0.770$ ,  $P=0.0001$ ). In human pulmonary artery smooth muscle cells (hPASMCs), kynurenine increased both cAMP and cGMP; in



intrapulmonary arteries, it relaxed the precontraction via NO/cGMP and cAMP pathways and in two models of established PH, it acutely decreased the mPAP. Our data suggest that kynurenine elevation might be specifically associated with mPAP; kynurenine acts on hPASMCs in synergy with NO and exerts acute pulmonary vasodilatation in chronic PH models. Therefore, kynurenine might provide both a new biomarker and a new therapeutic option for PH.

### **Pulmonary vascular component in chronic lung diseases**

Within the frame of cooperation with the Rehabilitation Clinic Bad Gleichenberg, we assessed the clinical characteristics and the potential pulmonary vascular abnormalities in over 400 patients with hypersensitivity pneumonitis. We found that patients presenting with both an increased estimated pulmonary arterial pressure and right heart dilatation in the echocardiography had decreased survival. In addition also patients with specific changes in their ECG indicating the presence of PH had decreased survival. These findings suggest that the presence of PH is an important determinant for prognosis in these patients. In 2017, the follow-up of patients was continued in order to observe long term changes of the pulmonary vasculature in this collective.

Our study investigating hemodynamics during exercise and the frequency of pulmonary complications in patients with Sjögren's syndrome was also continued in 2017; we altogether included 75 patients building one of the largest cohorts in this field. The study is planned to be finished in 2018 until the planned number of patients (n=100) and controls is reached.

## Early diagnosis of PH – the relevance of mildly elevated pulmonary arterial pressure

In order to understand the clinical relevance of mildly elevated mPAP, not fulfilling the definition of PH (mPAP>25 mmHg), in a real-world setting, we assessed the association of resting mPAP with all-cause mortality in a retrospective and a prospective cohort of patients with unexplained dyspnea and/or at risk of PH. After analyzing the data of almost 550 patients, CART analysis detected prognostic thresholds at a resting mPAP of 17 mmHg and 26 mmHg. Values between 20mmHg and 25mmHg represented an independent predictor of poor survival.

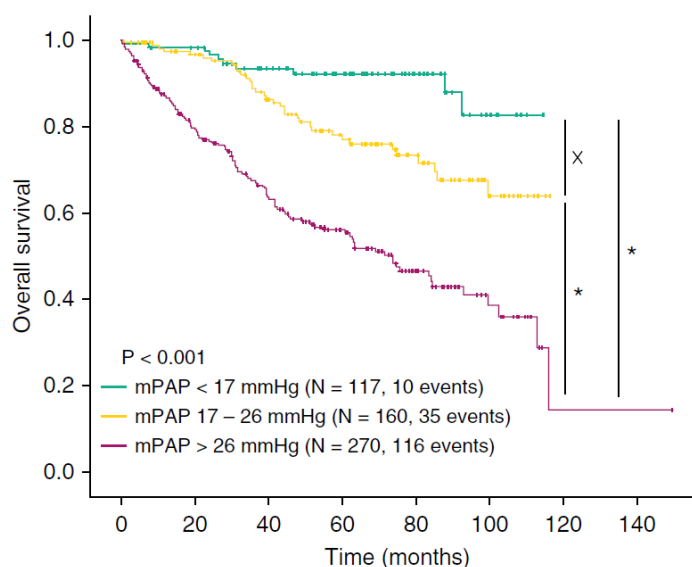


Figure 3: Univariate Kaplan-Meier survival analysis based on mean pulmonary arterial pressure (mPAP) groups from preset-free classification and regression tree analysis. \*P,0.001; X P = 0.003. (Douschan et al. AJRCCM 2018)

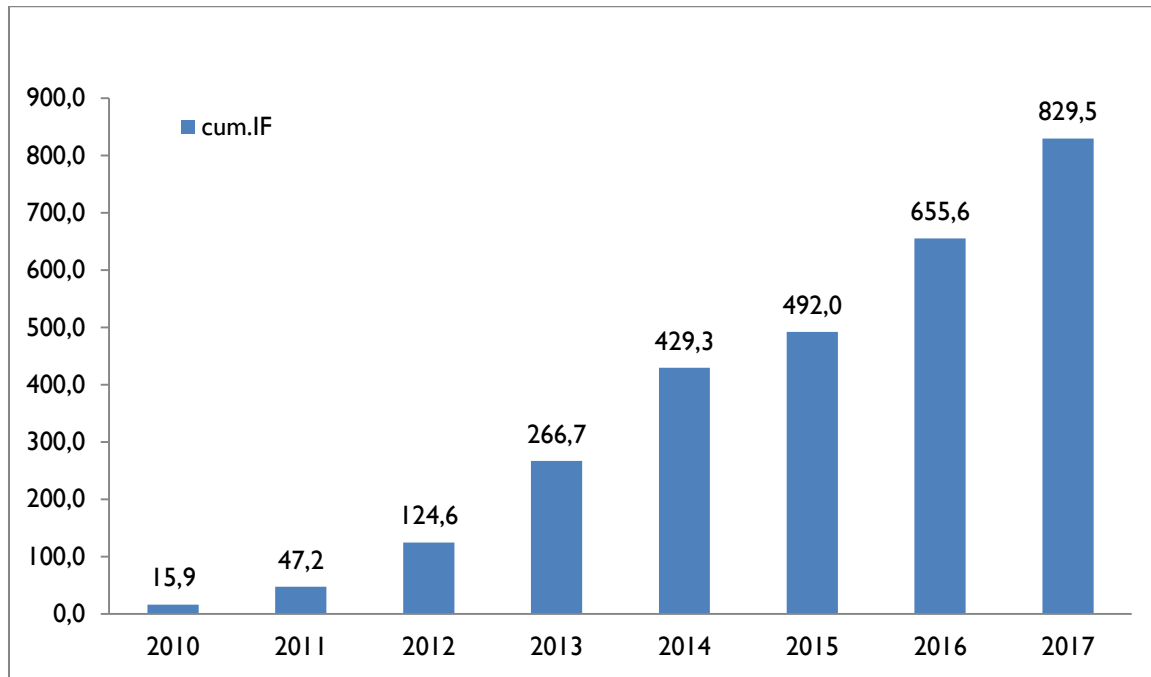
## Scientific Cooperations

AVIAN Alexander, Mag. Medical University of Graz, Austria  
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ULRICH Silvia, Prof. University of Zurich, Switzerland  
URSCHLER Martin, Dr. LBI for Clinic Forensic Imaging, Austria  
WUTTE Nora, Dr. Medical University of Graz, Austria

## 2.4 Publications of the LBI-LVR 2017

Starting in 2010 when our institute was first founded, the cumulative impact factor, an indicator for the quality of our scientific publications with LBI-LVR affiliation, reached the remarkable value of 830 by the end of the year 2017.



### 2.4.1 Original scientific publications

Bedau T, Peters F, Prox J, Arnold P, Schmidt F, Finkernagel M, Köllmann S, Wichert R, Otte A, Ohler A, Stirnberg M, Lucius R, Koudelka T, Tholey A, Biasin V, Pietrzik CU, Kwapiszewska G, Becker-Pauly C. Ectodomain shedding of CD99 within highly conserved regions is mediated by the metalloprotease meprin  $\beta$  and promotes transendothelial cell migration. *FASEB J.* 2017 Mar;31(3):1226-1237. IF 5.498.

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#### **2.4.2 Presentations at national and international conferences: oral communications**

Crnkovic S, et. al. Expansion of resident smc markers in the vascular remodelling; ATS conference, May 2017; Washington DC, USA.

Crnkovic S, et. al. Therapy of right ventricular fibrosis does not ameliorate right ventricular dysfunction. ÖGP 2017 - 41. Jahrestagung der Österreichischen Gesellschaft für Pneumologie, Oct 2017; Innsbruck, Austria.

Douschan P, et.al. Exercise hemodynamics in the screening for pulmonary vascular disease (PVD) in patients with portal hypertension – results from a prospective cross-sectional study. International Conference of the American-Thoracic-Society (ATS), May 2017; Washington DC, USA.

Douschan P, et.al. Impact of chronic liver disease on pulmonary hemodynamics and exercise tolerance – results from a prospective cross-sectional study. Annual meeting of the Austrian Society of Pneumology (ASP), Oct 2017; Innsbruck, Austria.

Douschan P, et. al. Exercise capacity and exercise hemodynamics in the screening for pulmonary vascular disease (PVD) in patients with portal hypertension – results from a prospective cross-sectional study. Annual Congress of the European Society for Studies of the Liver (EASL), Apr 2017; Amsterdam, Netherlands.

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Foris V, et. al. Pulmonale arterielle Hypertonie- Therapie Update 2017. Krankenhauspharmazie Update 2017, Jun 2017; Vienna, Austria.

Gungl A, et. al. Fra-2-driven interleukin-1 expression leads to pulmonary remodelling via interleukin-6 and tenascin C in systemic sclerosis. ATS conference, May 2017, Washington DC, USA.

Jandl K, et. al. Alterations in basement-membrane proteoglycans defines vascular remodelling in pulmonary hypertension associated with lung diseases. 6th FEBS Advanced Lecture Course, FEBS-MPTS, May 2017; Spetses, Greece.

Jandl K, et.al. Alterations in basement-membrane proteoglycans defines vascular remodelling in pulmonary hypertension associated with lung diseases. 6th FEBS Advanced Lecture Course, FEBS-MPTS, May 2017; Spetses, Greece.

Kovacs G, et. al. Annual Meeting of German CPET Society (Berlin) 2017: Pulmonary exercise hemodynamics, Apr 2017; Berlin, Germany.

Kovacs G, et. al. Hot topic: Pulmonary exercise hemodynamic. Annual Meeting of the German Cardiology Society, Apr 2017; Mannheim, Germany.

Kovacs G, et. al. Belastungshämodynamik: Implikationen für die Praxis?. PH-DACH Herbstsymposium der Deutschen Gesellschaft für Kardiologie, Oct 2017; Heidelberg, Germany.

Kovacs G, et. al. Belastungshämodynamik: Implikationen für die Praxis?. PH-DACH Herbstsymposium der Deutschen Gesellschaft für Kardiologie, Oct 2017; Heidelberg, Germany.

Kovacs G, et. al. PH– effects of medical treatment. DACH Congress for Pulmonary Rehabilitation, Jan 2017; Salzburg, Austria.

Kovacs G. et. al. Pulmonary hemodynamics during exercise – results of an ERS Task Force. ERS Congress, March 2017; Milan, Italy.

Kovacs G, et. al. Pulmonary hemodynamics during exercise – results of an ERS Task Force. Annual Meeting of the Austrian Respiratory Society, Oct 2017; Innsbruck, Austria.

Kovacs G, et. al. Pulmonary hemodynamics during exercise – results of an ERS Task Force. ERS Congress, March 2017, Milan, Italy.

Kovacs G, et. al. Pulmonary hemodynamics during exercise – results of an ERS Task Force. Annual Meeting of the Austrian Respiratory Society, Oct 2017, Innsbruck, Austria.

Kovacs G, et. al. Pulmonary Hypertension, acute pulmonary embolism, pulmonary vasculitis. ERS Summer School, Jan 2017, Barcelona, Spain.

Kovacs G, et. al. Pulmonary Hypertension, acute pulmonary embolism, pulmonary vasculitis. ERS Summer School, Jan 2017; Barcelona, Austria.

Kovacs G, et. al. Überblick über die aktuellen PAH Medikamente. PAH Patiententreffen, Oct 2017; Graz, Austria.

Kovacs G, et. al. Überblick über die aktuellen PAH Medikamente. PAH Patiententreffen, Oct 2017; Graz, Austria.

Kwapiszewska G, et. al. Increased Interleukin 1 are an early hallmark of pulmonary remodelling in Fra-2 mouse model of ssc. PVRI Annual World Congress, Jan 2017; Miami, USA.

Kwapiszewska G, et. al. Mystery of PASM, Feb 2017; Giessen, Germany

Odler B, et.al. Validation of cardiac MR parameters in the assessment of pulmonary hemodynamics. ERS, Oct 2017; Paris, France.

Olschewski A, et. al. Career development in medicine. Annual Meeting of Malvern College, March 2017; Great Malvern, UK.



Olschewski A, et. al. p22phox dependent NADPH oxidase in COPD and pulmonary hypertension, PVRI Annual World Congress, Jan 2017; Miami, USA.

Olschewski A, et. al. A Pro/Con Debate: Controversies in PAH Pathogenesis: PAH is NOT an Autoimmune Disease. ATS Conference, May 2017; Washington, USA.

Olschewski A, et. al. A TASK-1 in the lung: from cell biology to clinical implications Annual Meeting of the Hungarian Physiological Society & Hungarian Pharmacological Society and Hungarian Society for Vascular Biology, May 2017; Debrecen, HUNGARY.

Thekkekara Puthenparampil H, et. al. Differentially expressed lncRNAs in IPAH: the impact of PAXIP1-AS1 on human PASMC function. ÖGP 2017 - 41. Jahrestagung der Österreichischen Gesellschaft für Pneumologie, Oct 2017; Innsbruck, AUSTRIA.

Zabini D. PH-DACH Heidelberg, Session 7 Genetik und molekulare Medizin: TMEM als neues Target für reverse Remodeling. 2017, Heidelberg, Germany. [invited talk]

Zabini D. Die Effekte der Hypoxie auf die Lungengefäße –von Euler bis heute ; Effects of hypoxia on pulmonary circulation –from Euler to the present ÖGP2017 Innsbruck, Innsbruck, Austria. [invited talk]

### 2.4.3 Presentations at national and international conferences: posters

Biasin V, et. al. Idiopathic pulmonary arterial hypertension lungs possess distinct inflammatory profiles. Grover Conference, Oct 2017; Sedalia, USA.

Douschan P, et. al. Exercise capacity and exercise hemodynamics in the screening for pulmonary vascular disease (PVD) in patients with portal hypertension – results from a prospective cross-sectional study. Annual meeting of the European Agency for Studies of the Liver (EASL) 2017; Amsterdam, Netherlands.

Douschan P, et. al. Screening for pulmonary vascular disease (PVD) in patients with portal hypertension by investigating pulmonary hemodynamics during exercise. Annual Meeting of the European Respiratory Society (ERS) 2017; Milan, Italy.

Giuliani N, et. al. Fully-automatic Lung Fissure Detection from Thoracic Computed Tomography Images ÖGP 2017 - 41. Jahrestagung der Österreichischen Gesellschaft für Pneumologie, Oct 2017; Innsbruck, Austria.

Marsh LM, et. al. Idiopathic pulmonary arterial hypertension lungs possess distinct inflammatory profiles. ATS conference; May 2017, Washington DC, USA.

Nagy B, et. al. Kynurenine Causes Pulmonary Arterial Relaxation in Pulmonary Hypertension. American Journal of Respiratory and Critical Care Medicine 2016 - Experimental Biology conference, Apr 2017; Chicago, USA

Pienn M, et. al. Age-related changes in lung vessel morphology in healthy men and women; ÖGP 2017 - 41. Jahrestagung der Österreichischen Gesellschaft für Pneumologie, Innsbruck, Austria.

Thekkekara Puthenparampil H, et. al. Differentially expressed lncRNAs in IPAH: the impact of PAXIP1-AS1 on human PASMC function. ÖGP 2017 - 41. Jahrestagung der Österreichischen Gesellschaft für Pneumologie, Oct 2017; Innsbruck, AUSTRIA.

Zabini, D et. al. W.M. SMAD3 contributes to lung vascular remodeling in pulmonary arterial hypertension via MRTF disinhibition, Experimental Biology conference, Apr 2017; Chicago, USA

#### 2.4.4 Other papers

Hoffmann J, Wilhelm J, Kwapiszewska G. Laser Capture Microdissection of Tissue Sections for High-Throughput RNA Analysis. Methods Mol Biol. 2017. IF 0.79.

Foris V. et al. Pulmonale Hypertonie. Pneumologie 2017;14:117–128. IF 0.07.

Horvath I, Kovacs G, Munteanu O, Kmyta V, Midulla F, Kadam S, Rumman N. Summer schools of adult and paediatric respiratory medicine: course report. Breathe 2016; 12:305–308. IF 0.41.

Jandl K, Heinemann A. The therapeutic potential of CRTH2/DP2 beyond allergy and asthma. Prostaglandins Other Lipid Mediat. 2017 Aug 14. IF 2.640.

Kovacs G, Avian A, Foris V, Tscherner M, Kqiku X, Douschan P, Bachmaier G, Olschewski A, Matucci-Cerinic M, Olschewski H. Use of ECG and Other Simple Non-Invasive Tools to Assess Pulmonary Hypertension. PLoS ONE 2016;11(12): e0168706. IF 2.806

Kovacs,G. et al. Screening auf pulmonale Hypertonie. Pneumologie 2017; March 15. IF 0.07.

Kovacs, G; Olschewski, H. Screening in pulmonary hypertension. PNEUMOLOGIE. 2017; 14(3): 153-159.

Sill H, Kqiku-Kryeziu X, Avian A, Kovacs G, Gaal S, Zebisch A, Olschewski H. Pulmonary arterial pressure in patients with myelodysplastic syndromes. Leuk Lymphoma. 2016 Nov;57(11):2723-6. IF 2.755.

Wohlkoenig C, Leithner K, Olschewski A, Olschewski H, Hrzenjak A. TR3 is involved in hypoxia-induced apoptosis resistance in lung cancer cells downstream of HIF-1 $\alpha$ . Lung Cancer. 2017 Sep;111:15-22 IF 4.3.

## 3 Research made in Austria

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Several of our colleagues received prestigious travel scholarship which allowed the acquisition of new experience and methodologies in the renowned research groups around the world. Here they briefly describe their experience:

### 3.1 Inside LBI-LVR: Anna Gungl

#### Experience Report – Research stay in Berlin



In the past year, I had the opportunity to spend two months in Berlin at the laboratory of Prof. Martin Witzentrath in the Department of Infectious Diseases and Pulmonary Medicine at the Charité in Berlin. This short-term research fellowship was funded by the European Respiratory Society (ERS) and gave me the opportunity to work on a joint project entitled “The role of infections in acute respiratory worsening in lung fibrosis”. During my time in Berlin, I learned several new methods and got to know new models of pulmonary inflammation. Coming from a background of molecular biology, I

especially liked that most of the researchers in Prof. Witzentrath’s group have a medical or veterinary background which led to a fruitful exchange of knowledge. It was great fun and very informative to discuss different methods and scientific questions with other young researchers from a different field of expertise.

From a personal point of view it was great to meet such nice new people and to experience a big city like Berlin. I fell in love with the street food markets, which pop up everywhere on the weekends and have amazing food from all over the world. As a small-town girl, I was surprised how quickly I felt at home. I will definitely revisit this wonderful city and the friends I made there!

### 3.2 Inside LBI-LVR: Helene Thekkekara Puthenparampil

#### About my research stay in Cambridge and Freiburg



Last year I had the honor of receiving the ÖGP Short Term Fellowship Grant, which I was glad to use for a bioinformatics workshop in Cambridge and a research stay at the University Medical Center of Freiburg. The workshop was very well organized by the European Bioinformatics Institute (EMBL-EBI) and was directed at young researchers that need to work with large biological databases. Taking part in this program, I could acquire up-to-date expert

knowledge on working with large amounts of biological data. The workshop was visited by a variety of researchers from multidisciplinary research areas which not only promoted vivid conversations during the breaks in-between courses, but also encouraged networking and gave me the opportunity to make many new friends. The stay in Freiburg, at Dr Mussolino's lab was all about learning a new technique. Thanks to advance email correspondence with the lab, I could not only prepare theoretical basis beforehand, but also arrange all pre-experimental steps from home according to needs and so take full advantage of the time I was allowed to spend in the foreign lab. In Freiburg I recieved a very profound introduction to the background and methodologies of the technique. I was well accommodated into their research group and received first hand advices from the leading experts from the field. The two weeks stay gave me an opportunity to see how another similarly motivated lab works, allowed me to notice differences in the organization and functionality of the labs, see the respective (dis-)advantages. Making new acquaintances and interacting with them, I could learn about other researchers, their paths of career and personal growth which also gave light to new perspectives in my mind. Generally, I strongly recommend a research stay abroad in a new environment to any student, if possible. I surely profited from this experience and would like to thank ÖGP and LBI for all kinds of support. Thank you!

### 3.3 Inside LBI-LVR: Diana Zabini

#### Why going abroad?



I had the great opportunity to go with an Erwin Schrödinger Stipend from the FWF to Toronto, Canada and work in Prof. Wolfgang Kueblers Laboratory at the St. Michaels hospital in the field of pulmonary hypertension. While I was preparing for my two years abroad I was of course excited and multiple questions were in my head, such as: how will it be in another country, how is the research facility, how are the people etc. It is this excitement which activates and revives you! When thinking back of my arrival in Toronto I remember feeling immediately at home. I enjoyed soaking up the new impressions of the city. People were amazing, supportive and welcoming! The scientific exchange in the St. Michael's hospital was great. I met great people, built new friendships which turned also into great scientific collaborations and boosted my research career. It was great to see how laboratories work in different countries; there I got to know the so called open lab space culture. This means several groups are working in one big room with several work benches and some equipment are shared. In that way you get easily in contact with colleagues from different disciplines and creativity can start from there. To move out from your comfort zone activates you in a certain way: you have to orient yourself newly, adjust to new situations, and find contact persons whom you

can ask for experimental or technical advice or where to go after work or what to do on the weekend 😊 . Being abroad opens you up for new possibilities and widens your horizon. I would recommend everyone to use the opportunity to experience some time away from your home country!



# 4 Teaching and Training Activities of the Institute

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## 4.1 Training in the LBI for Lung Vascular Research

### 4.1.1 Training of the LBI-LVR Staff

The following advanced training courses were offered in 2017:

Name	Affiliation	Title of the Lecture/ Workshop
Seyens Ltd, Jernej Zupanc, Dr.	SI-1000, Ljubljana	Workshop: Effective Visual Communication of Science
FWF Der Wissenschaftsfond	FWF Austrian Science Fund, Wien Austria	FWF Coaching Workshop
	Ludwig Boltzmann Gesellschaft	Value Capture Workshop
TIEDE Katherine, Dr.	Scientific Communication Seminars and Consulting, Graz, Austria	Scientific Writing Workshop
Ludwig Boltzmann Gesellschaft	Wissenschaft im Dialog gGmbH ( <a href="http://www.wissenschaft-im-dialog.de">www.wissenschaft-im-dialog.de</a> )	Summer School “Wissenschaft kommunizieren!”
Medical University of Graz	Medical University of Graz, Austria	Teaching in English

### 4.1.2 LBG Career Center in Graz July 2017

The LBG Career Center visited our institute on July 19th, 2017. Dr. Verena Aichholzer gave an overview about the concept of the LBG Career Center.



### 4.1.3 Invited Speakers 2017

FARBER Harrison, Prof.	Pulmonary Hypertension Center, Boston University	03 MAR 17	Contradiction and Update in Reveal Register
D'ALTO Michele, Prof.	Department of Cardiac Thoracic and Respiratory Sciences, Second University of Naples	24 MAR 17	Exercise Echo and Differentiation of HfpEF with Imaging
KIRSTEN Detlef, Prof.	LungenClinic Grosshansdorf, Germany	06 JUN 17	Contradiction and Update in Reveal Register
ALLANORE Yannick, Prof.	Paris Descartes University, Paris,	21 SEP 17	Systemic Sclerosis and the Lung: hot topics and future directions from the clinic and from the research laboratory
WILHELM Jochen, PhD.	Justus-Liebig-University, Gießen	03 OCT 17	Introduction to Linear Models
ANTIGNY Fabrice, PhD	French Institute of Health and Medical Research (INSERM), Paris	17 OCT 17	KCNK3 channels in pulmonary arterial hypertension
DORFMÜLLER Peter, Prof.	Marie Lannelongue Hospital, Paris-South University, Le Plessis Robinson, France	21 NOV 17	Crossroads, connections and similarities in PH pathology
VESELY Paul, PhD	Medical University of Graz, Diagnostic & Research Center for Molecular BioMedicine Institute of Pathology	17 DEC 17	LipoLUNG, Pathological lung phenotype of mice lacking Adipose Triglyceride Lipase