Ludwig Boltzmann Institute
Lung Vascular Research

ANNUAL REPORT

2015

Content

Ludwig Boltzmann Institute for Lung Vascular Research

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Ludwig Boltzmann Institute for Lung Vascular Research

1. The Institute in Overview

The Ludwig Boltzmann Institute for Lung Vascular Research (LBI-LVR) is a non-profit research institute founded in July 2010 by the Ludwig Boltzmann Gesellschaft (LBG) - an Austrian non-university research organisation who acts as carrier institution for Ludwig Boltzmann Institutes. The institutes conduct research in the field of Medicine & Life Sciences and in the field of Humanities. The LBI for Lung Vascular Research was established after a demanding two-stage evaluation by international peers who strongly recommended the founding of the institute.

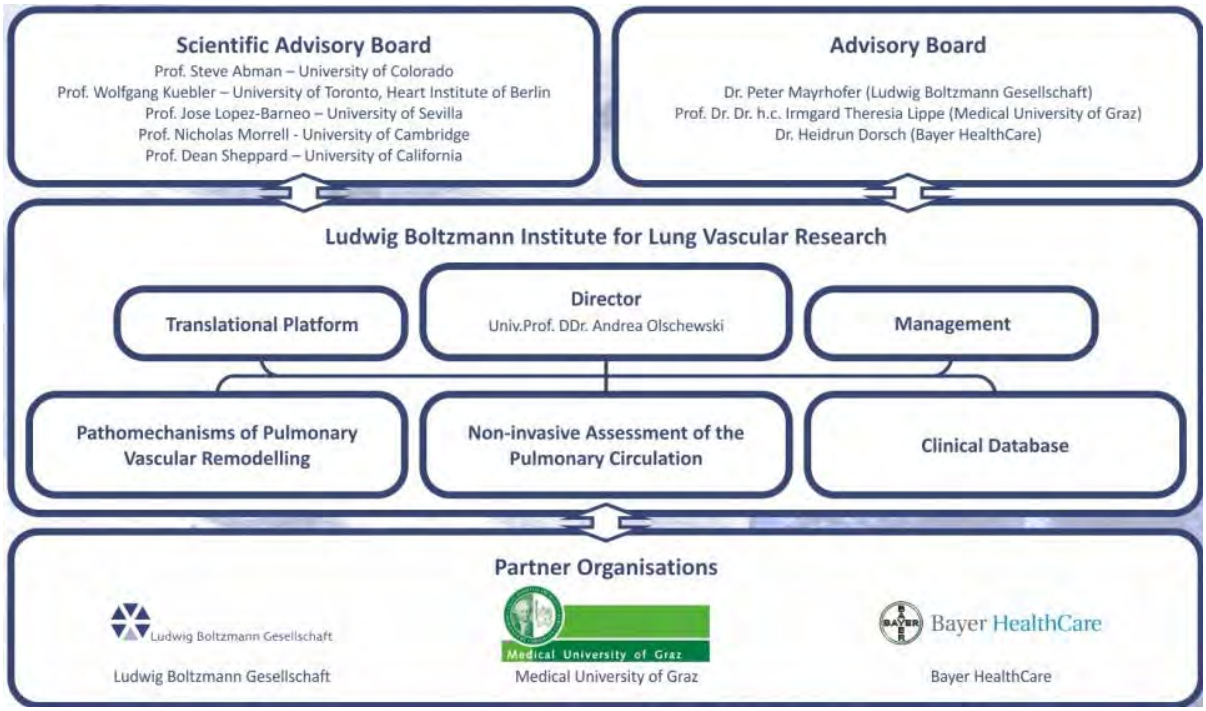
The LBI-LVR, like the other Ludwig Boltzmann Institutes, is established on a partnership between organisations and institutes that traditionally carry out research and organisations that traditionally apply research. The LBI-LVR Consortium currently comprises the Ludwig Boltzmann Gesellschaft as carrier institution in partnership with the Medical University of Graz (MUG) and Bayer HealthCare. The Advisory Board of the LBI-LVR, composed of the representatives of the partner organisations (LBG, MUG, and Bayer Austria) supervises the progress of the LBI-LVR. The Scientific Advisory Board (SAB) of the LBI-LVR is an independent, world-wide recognised group of experts in pulmonary vascular biology and in pulmonary hypertension monitoring 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 Centre 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 Centre 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

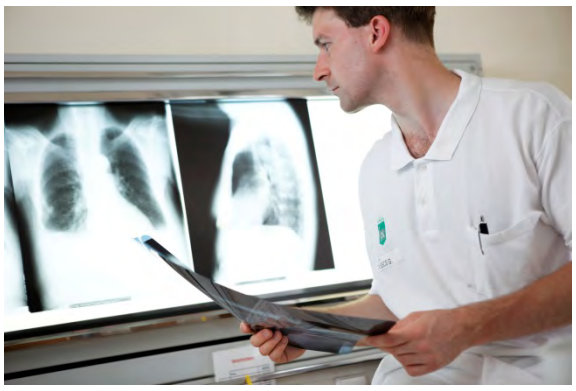


LBI-LVR annual retreat, Riegersburg 19.06.2015 (Copyright: LBI-LVR/ Kainz)

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. Over the past 15 years, the diagnostics and therapy of the prototype disease pulmonary hypertension (PH) have made tremendous progress. This continued in 2014, as landmark studies led to the introduction of novel drugs and therapy concepts. However, PH remains in many cases a notoriously under-diagnosed chronic and fatal disease. That is why early recognition of the disease is still one of the major challenges. As the diagnosis of PH is done by the 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 actual challenge is PH in heart and lung diseases: large patient populations with severe heart failure and chronic obstructive lung disease may develop PH during the course of their disease. At the moment effective treatment is still missing for these conditions.

Progressive loss of exercise capacity and worsening dyspnoea represent the most common symptoms of the disease. 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 for Lung Vascular Research 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 disease 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. Partners of the Institute

We thank our partners, the Ludwig Boltzmann Society as well as the Government of Austria for their continuous support.

Ludwig Boltzmann Society (http://www.lbg.ac.at/en)

The Ludwig Boltzmann Gesellschaft (LBG) is a non-profit sponsor of research establishments in Austria. It is named after the Austrian physicist, mathematician and philosopher Ludwig Boltzmann, whose broad scientific interests still remain the basis for the interdisciplinarity 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/)

The Medical University of Graz (MUG) has declared to enhance research on vascular diseases ("kardiovaskuläres Forschungsfeld" or "focus on cardio-vascular research") giving highest priority for this field of interest. Research activities of the 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 Health Care (http://www.bayerhealthcare.com/scripts/pages/en/)

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

1.4. Scientific Advisory Board and Advisory Board

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

Prof. Wolfgang Kuebler – University of Toronto, Canada

Heart Institute of Berlin, DE

Link:
http://www.stmichaelshospital.com/research/profile.php?id=kuebler&

Prof. Steve Abman – University of Colorado, US

Link:
http://www.ucdenver.edu/academics/colleges/medicalschool/departments/pediatrics/research/programs/phlc/Pages/PediatricHeartLungCenter.aspx

Prof. Nick Morrell – University of Cambridge, UK

Link: http://www.med.cam.ac.uk/morrell/

Prof. Jose Lopez-Barneo – University of Sevilla, ES

Link: http://www.us.es/

Prof. Dean Sheppard – University of California, US

Link: http://pulmonary.ucsf.edu/index.html

Advisory Board of the Partners (Board) – chaired by Prof. Irmgard Theresia Lippe

Prof. Dr. Dr.h.c. Irmgard Theresia Lippe, Medical University of Graz

https://forschung.medunigraz.at/fodok/suchen.person_uebersicht?sprache_in=de&menue_id_in=101&id_in=90242960

Dr. Peter Mayrhofer, Ludwig Boltzmann Gesellschaft

http://www.lbg.ac.at/de/team/dr-peter-mayrhofer

Dr. Heidrun Dorsch, Bayer Health Care

http://healthcare.bayer.com/scripts/pages/en/

The SAB-Meeting took place in Graz on July 9th and 10th, 2015. The meeting started with a scientific overview on the first meeting day followed by the scientific presentations on the second meeting day.

Copyright: LBI-LVR

The Board Meeting took place in Graz on November 19th, 2015.

1.5. Personal and Human Resources Development

a) The LBI-LVR Staff

The LBI-LVR staff consists of the director, the programme 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.

Name	Entry	Function
Avian Alexander, Univ.-Ass. Mag.rer.nat. Dr.rer.nat.	9/11	Statistician. Affiliation: Institute for Medical Informatics, Statistics, and Documentation at the Medical University of Graz (MUG). He supports the study design at our institute.
Bálint Zoltán, PD Dr. PhD	9/10	Group leader of the team "Non-invasive assessment of the pulmonary circulation". His responsibilities include the planning and coordination of studies for the development of a quantitative, non-invasive and reproducible technique for the assessment of the pulmonary circulation.
Biasin Valentina, PhD MSc	10/10	Junior scientist / PhD student of the Doctoral programme Molecular Medicine at the MUG. Her primary task is the role of proteases in PH development. She successfully finished her PhD in our institute in November 2014.
Blanz Elisabeth, BSc	1/15	Associated technician as a member of the Experimental Anaesthesiology. Affiliation: Experimental Anaesthesiology, Department of Anaesthesiology and Intensive Care Medicine of the MUG. She supports the research activities of the Experimental Anaesthesiology. Her work mainly comprises protein and RNA analyses, experiments with various cell lines and siRNA-transfections as well as histological stainings.
Braunschmid Verena, MSc	5/15	Technician of the group "Pathomechanisms of pulmonary vascular remodelling". She does the isolation and cultivation of various cell lines, immunohistochemical stainings and assays, performs experiments with the isolated-perfused lung model and molecularbiological work and is responsible for data analysis.

Crnkovic Slaven, PhD DI	10/11	Post-Doc Researcher. His research focus is the chronic vascular remodelling.
Douschan Philipp, Dr.med.univ.	8/13	Junior scientist / Dr.sci.med. student and physician at the Division of Pulmonology at the MUG. He is responsible for the clinical databank and supports the team with his expertise in pulmonary hypertension and lung diseases.
Egemnazarov Bakytbek, PhD	11/11	Post-Doc Researcher. His research focus is the characterisation of right heart hypertrophy.
Foris Vasile, Dr. med. univ.	10/10	Junior scientist / PhD student of the Doctoral programme Molecular Medicine at the MUG and physician at the Division of Pulmonolgy at the MUG. He focusses on PH biomarkers.
Fuchs Thomas, MSc	3/13	Technician. He supports the translational platform with cell culture experiments and with the isolated-perfused lung model. He performs cell culture assays, molecular biological techniques, and immunohistochemistry.
Ghanim Bahil, Dr. med. univ.	10/11	Junior scientist and physician at the the Medical University of Vienna (MUV). Affiliation: Department of Thoracic Surgery at the MUV. He supports the institute in human tissue sampling.
Gleixner Christina, MSc	10/14 – 9/15	Technician. Her tasks comprise molecular-biological examinations, immunohistochemistry, cell culture and cell culture assays as well as data evaluation.
Götz Camilla, MSc	5/15	Technician of the group “Pathomechanisms of pulmonary vascular remodelling”. She works with the isolated-perfused lung model and performs the cultivation of various cell lines. Furthermore, she is responsible for cell culture assays, molecularbiological procedures and immuno-histochemistry.
Gruber Fabian	6/15	Student assistant in the team of Dr. Kovacs. His main task is patient data input and maintenance.
Gungl Anna, BSc MSc.	9/14	Junior scientist / PhD student of the Doctoral Programme Molecular Medicine at the MUG. She focuses on metalloproteases in tissue remodelling.
Halsegger Sabine	maternity leave	Associated technician. Affiliation: Experimental Anaesthesiology, Department of Anaesthesiology and Intensive Care Medicine of the MUG. She supports the research activities of the Experimental Anaesthesiology.

Hoffmann Julia, Dipl.-Biol. Dr.	03/12	Post-Doc Researcher. Her focus is the examination of the signal pathways via microarrays.
Hrzenjak Andelko, Assoc. Prof. PD Dr.rer.nat.	9/10	Senior scientist and assistant professor at the Division of Pulmonology at the MUG. He supports our institute in the field of proteomics.
Jakob-Pelikan Claudia	12/12	Assistant of the LBI director. Responsible for administrative tasks.
Kainz Stefanie, MA	1/13	Assistant of the LBI-IVR director. Her duties comprise the support of the budgetary planning, financial reports, personnel management, and the organisation of meetings and events.
Kleinschek Daniela, Dr. Mag. phil.	12/12	Study nurse supporting the clinical study group in coordination of the clinical studies, patient care, documentation, and data archiving. Furthermore, she has initiated and is responsible for the Newsletter for our patients and their relatives.
Kovacs Gabor, PD Dr.med.	10/10	Group leader of the team “Clinical database”.
Kwapiszewska Grazyna, PD Dr.	11/10	Deputy Director of the LBI-LVR and group leader of the team “Pathomechanisms of pulmonary vascular remodelling”.
Leithner Katharina, Univ.-Ass. Dr.med.univ. PhD	10/14	Associated junior scientist / PhD student of the Doctoral programme Molecular Medicine at the MUG. She has successfully completed her PhD study about the role of phosphoenolpyruvate carboxykinase in lung cancer and currently supports the research groups in metabolomics.
Marsh Leigh, Dr. MSc	1/11	Leader of the translational platform.
Mischkulnig Lena, BSc	2/15 – 10/15	She made her Master thesis entitled: „The role of Angptl4 in profibrotic remodelling“.
Nagaraj Chandran, MSc PhD	4/11	Post-Doc Researcher. His research focus is the regulation of pulmonary vasoconstriction.
Nagy Bence, MSc	10/14	Junior scientist / PhD student of the Doctoral programme Molecular Medicine at the MUG. He focusses on the role of transporters and metabolomic pathways in pulmonary hypertension.
Oberreiter Lisa Maria, MSc	2/14	Technician. Here duties cover diverse cell isolations from human lungs. She also performs cell culture experiments as well as molecular biology techniques, cell and tissue staining.

Odler Balazs, Dr. med. univ.	10/15	Researcher in the group “Clinical database” who supports the scientific work of the team leader Gabor Kovacs.
Olschewski Andrea, Univ.-Prof. Dr. med.	7/10	Director of the LBI-LVR.
Olschewski Horst, Univ.-Prof. Dr. med.	7/10	Head of the Division of Pulmonology at the MUG. He supports the planning of the translational and clinical studies.
Papp Rita, Dr.	9/12	Post-Doc Researcher. She investigates the role of ion channels via molecularbiological and electrophysiological methods e.g. patch-clamp.
Payer Christian, MSc	2/15 – 7/15	Master student in the group “Non-invasive assessment of the pulmonary circulation” who does the separation of arteries and veins in lung CT-images.
Pfeiffer Susanne, Dr.med.univ. BSc	4/15	Researcher in the group “Clinical database” who supports the scientific work of the team leader Gabor Kovacs.
Pienn Michael, Dipl.-Ing.	10/10	Junior scientist / PhD student at the Graz University of Technology. His focus is the dynamic assessment of the pulmonary circulation and computed tomography image analysis.
Reinisch Sabrina, BSc	maternity leave	Technician.
Sahu-Osen Anita, PhD MSc	12/15	Post-Doc Researcher. She supports the group of Dr. Kwapiszewska working for the FWF project "The Role of transcription factor Fra-2 in pulmonary hypertension".
Schittl Julia	12/10	Technician supporting the research activities in the group of Dr. Kwapiszewska.
Schloffer Maria		Associated technician. Affiliation: Department of Anaesthesiology at the MUG. She supports the research activities of the Experimental Anaesthesiology.
Sharma Neha, MSc	11/12	Assoc. MUG PhD student supporting Prof. Andrea Olschewski.
Stacher-Priehse Elvira, PD Dr. med. univ.	9/10	Senior scientist and pathologist of the Department of Pathology at the MUG. She supports the institute in issues regarding lung histology.

Tischler Simone, MSc	1/14	Associated technician of the MUG. Affiliation: Department of Anaesthesiology and Intensive Care Medicine. She supports the research activities of the Experimental Anaesthesiology. Her tasks mainly comprise protein and RNA analyses, cell culture and various histological staining techniques.
Tornyos Adrienn, Dr.	9/15	Assoc. MUG scientist in the team of Dr. Kovacs.
Wakonigg Gudrun, Mag. Dr.rer.nat.	3/12	PR assistant of the LBI-LVR director. Her tasks comprise press releases, the maintenance of the LBI website as well as the release of the annual reports.

b) Scientific accomplishments in 2015

In 2015, three colleagues did their habilitation and one Master student graduated:

Name	**Habilitations 2015**
STACHER-PRIEHSE Elvira	Habilitation: Modern age pathology of pulmonary arterial hypertension Graduation on 10 FEB 2015 Current status: maternity leave
BÁLINT Zoltán	Habilitation: Non-invasive diagnosis of pulmonary hypertension with computed tomography Graduation on 9 APR 2015 Current status: Group Leader in the LBI-LVR
KWAPISZEWSKA Grazyna	Habilitation: Mechanisms of vascular remodelling in pulmonary hypertension Graduation on 3 JUN 2015 Current status: Group Leader and Deputy Director in the LBI-LVR
Name	**Master/Diploma Theses 2015**
PAYER Christian	Master Thesis: Separation of arteries and veins in pulmonary CT images Final exam on 28 MAY 2015 Current status: PhD-Student, Cooperation TU Graz and LBI for Clinical-Forensic Imaging, Austria

c) Awards and prices

We proudly announce that some of your colleagues were granted with awards:

Name	Awards 2015
BIASIN Valentina	PH UP2DATE Award, Munich, Germany
BIASIN Valentina	Michael Neumann Gedächtnispreis 2015, Graz, Austria
BIASIN Valentina	1st Poster Award, PH-DACH Symposium Heidelberg, Germany
CRNKOVIC Slaven	PH UP2DATE Award, Munich, Germany
CRNKOVIC Slaven	1st Poster Award, PH-DACH Symposium Heidelberg, Germany
CRNKOVIC Slaven	Short Term Fellowship of the EU initiative COST
EGEMNAZAROV Bakytbek	2nd Poster Award, 4. Forschungswerkstatt – "Pulmonary Hypertension", Berlin, Germany
GUNGL Anna	ÖGP Short Term Fellowship 2015, Graz, Austria
GUNGL Anna	1st Poster Award, PH-DACH Symposium Heidelberg, Germany
HOFFMANN Julia	René Baumgart-Research Award, Berlin, Germany
KWAPISZEWSKA Grazyna	1st Poster Award, PH-DACH Symposium Heidelberg, Germany
MARSH Leigh	1st Poster Award, PH-DACH Symposium Heidelberg, Germany
OLSCHEWSKI Andrea	1st Poster Award, PH-DACH Symposium Heidelberg, Germany
PAPP Rita	2nd Poster Award, 4. Forschungswerkstatt – "Pulmonary Hypertension", Berlin, Germany
PAYER Christian	2nd Place of the ÖGP Scientific Poster Award for Basic Research, Graz, Austria
PAYER Christian	Student Bursary Award of the 18th MICCAI Conference, Munich, Germany
PIENN Michael	Best Oral Presentation Award of MIUA 2015, Lincolnshire, UK

d) Training of the LBI-LVR Staff

The following team members successfully joined advanced training courses in 2015:

Name	Date	Course
BÁLINT Zoltán	Feb 2015	Presentation Skills Training, Dr. Isabel Landsiedler, Graz, Austria
BÁLINT Zoltán	Sep 2015	Rhetorical Training, Dr. Isabel Landsiedler, Graz, Austria
BÁLINT Zoltán	Dec 2015	Media Training of Mona Decker-Mathes & Peter Mathes, Mariatroster Bildungshaus, Graz, Austria
BIASIN Valentina	Feb 2015	Presentation Skills Training, Dr. Isabel Landsiedler, Graz, Austria

CRNKOVIC Slaven	Feb 2015	Presentation Skills Training, Dr. Isabel Landsiedler, Graz, Austria
DOUSCHAN Philipp	Feb 2015	Presentation Skills Training, Dr. Isabel Landsiedler, Graz, Austria
DOUSCHAN Philipp	Mar 2015	Advanced Training in Echocardiography, German Society for Ultrasound in Medicine, Leipzig, Germany
DOUSCHAN Philipp	Apr 2015	Training in Spiroergometry, DGIM, Mannheim, Germany
DOUSCHAN Philipp	Apr 2015	GCP – Performance of Clinical Studies, Medical University of Graz, Austria
DOUSCHAN Philipp	Apr 2015	Strain Imaging Echo Course, International Academy of Ultrasound, Berlin, Germany
DOUSCHAN Philipp	Sep 2015	Basic Respiratory Mechanics, ERS, Amsterdam, Netherlands
DOUSCHAN Philipp	Sep 2015	Advanced Respiratory and Cardiovascular Testing, ERS, Amsterdam, Netherlands
DOUSCHAN Philipp	Sep 2015	Referral Guidelines for Lung Transplantation, ERS, Amsterdam, Netherlands
EGEMANZAROV Bakytbek	Feb 2015	Presentation Skills Training, Dr. Isabel Landsiedler, Graz, Austria
FORIS Vasile	Feb 2015	Presentation Skills Training, Dr. Isabel Landsiedler, Graz, Austria
GUNGL Anna	Feb 2015	Presentation Skills Training, Dr. Isabel Landsiedler, Graz, Austria
GUNGL Anna	Apr 2015	FELASA B, Medical University of Graz, Austria
HOFFMANN Julia	Feb 2015	Presentation Skills Training, Dr. Isabella Landsiedler, Graz, Austria
HRZENJAK Andelko	Feb 2015	Presentation Skills Training, Dr. Isabel Landsiedler, Graz, Austria
HRZENJAK Andelko	Sep 2015	Rhetorical Training, Dr. Isabel Landsiedler, Graz, Austria
KAINZ Stefanie	Jan 2015	English for non-scientific staff, Centre for Language, Plurilingualism und Language Didactics Graz, Austria
KAINZ Stefanie	Apr 2015	Leading and Motivating without Managerial Authority, WIFI Unterpremstätten, Austria
KAINZ Stefanie	Dec 2015	Media Training of Mona Decker-Mathes & Peter Mathes, Mariatroster Bildungshaus, Graz, Austria
KLEINSCHEK Daniela	APR 2015	GCP – Performance of Clinical Studies, Medical University of Graz, Austria

KLEINSCHEK Daniela	May 2015	„Mental fitness into age“ by Prof. Reinhold Schmidt, KAGES, Graz, Austria
KLEINSCHEK Daniela	Jul 2015	„Use of medical samples and data“, Medical University of Graz, Austria
KLEINSCHEK Daniela	Dec 2015	Seminar "Biological rhythms and resilience“, Medical University of Graz, Austria
KOVACS Gabor	Feb 2015	Presentation Skills Training, Dr. Isabel Landsiedler, Graz, Austria
KOVACS Gabor	Sep 2015	Rhetorical Training, Dr. Isabel Landsiedler, Graz, Austria
KWAPISZEWSKA Grazyna	Feb 2015	Presentation Skills Training, Dr. Isabel Landsiedler, Graz, Austria
KWAPISZEWSKA Grazyna	Sep 2015	Management Workshop of the Ludwig Boltzmann Society, Dürnstein, Austria
KWAPISZEWSKA Grazyna	Sep 2015	Rhetorical Training, Dr. Isabel Landsiedler, Graz, Austria
KWAPISZEWSKA Grazyna	Dec 2015	Media Training of Mona Decker-Mathes & Peter Mathes, Mariatroster Bildungshaus, Graz, Austria
KWAPISZEWSKA Grazyna	Feb 2015	Professorship Application Course, Karl-Franzens University of Graz, Austria
LEITHNER Katharina	Feb 2015	Presentation Skills Training, Dr. Isabel Landsiedler, Graz, Austria
MARSH Leigh	Feb 2015	Presentation Skills Training, Dr. Isabel Landsiedler, Graz, Austria
MARSH Leigh	Sep 2015	Rhetorical Training, Dr. Isabel Landsiedler, Graz, Austria
MISCHKULNIG Lena	Feb 2015	Presentation Skills Training, Dr. Isabel Landsiedler, Graz, Austria
NAGARAJ Chandran	Feb 2015	Presentation Skills Training, Dr. Isabel Landsiedler, Graz, Austria
NAGY Bence	Feb 2015	Presentation Skills Training, Dr. Isabella Landsiedler, Graz, Austria
OLSCHEWSKI Andrea	Feb 2015	Presentation Skills Training, Dr. Isabel Landsiedler, Graz, Austria
OLSCHEWSKI Andrea	Sep 2015	Management Workshop of the Ludwig Boltzmann Society, Dürnstein, Austria
OLSCHEWSKI Andrea	Sep 2015	Rhetorical Training, Dr. Isabel Landsiedler, Graz, Austria

PAPP Rita	Feb 2015	Presentation Skills Training, Dr. Isabel Landsiedler, Graz, Austria
PAYER Christian	Feb 2015	Presentation Skills Training, Dr. Isabel Landsiedler, Graz, Austria
PIENN Michael	Feb 2015	Presentation Skills Training, Dr. Isabel Landsiedler, Graz, Austria
PIENN Michael	Mar 2015	Optimised Imaging of the Small-Animal Lung Vasculature, VU University Medical Centre, Amsterdam, The Netherlands

1.6. Our Habilitations 2015

Elvira Stacher-Priehse: „ Modern age pathology of pulmonary arterial hypertension “


Copyright: LBI-LVR

Abstract of the Habilitation thesis:

Pulmonary hypertension (PH) is associated with characteristic histopathologic alterations of the pulmonary arteries. This work aimed on the description of changes of the pulmonary vasculature in explanted lungs of patients suffering from PH as well as in controls in the era of modern therapeutics. It was the first published study based on a standardised protocol for harvesting tissue in a systematic and uniform way. The histologic findings were correlated with various clinical parameters. It could be demonstrate that all PH lungs showed marked vascular remodelling, mainly affecting the intima. Interestingly, there was a huge overlap of the media thickness in PH patients and controls, in fact approximately in 90% of the measurements. This finding is of clinical importance, since the postulate of the pronounced media thickening in PH led to the implementation of mainly vasodilatative drugs; in fact, at the moment the thickened intima cannot be therapeutically influenced. Regarding clinical parameters, it could be demonstrated that the media thickness correlates with both the mean pulmonary arterial pressure (mPAP) and the pulmonary vascular resistance (PVR). Female patients show significantly more profiles of plexiform lesions than males. Histopathologic patterns allow a segregation of PH lungs in categories of idiopathic pulmonary arterial hypertension, associated pulmonary hypertension as well as venooclusive disease. Lungs with BMPRII mutation (Bone Morphogenetic Protein Receptor 2) show an extremely thickened media; this association was shown for the first time. PH lungs were stratified in quartiles according to their degree of vascular remodelling – here it could be shown that there was no association of remodelling and the number of plexiform lesions. In general, an impressive variability of vascular changes between lungs and within a given lung was encountered. Pertaining to medication, specific changes attributable to a certain substance could not be found, however, the number of profiles of plexiform lesions correlated positively with the use of prostacyclins. Frequently, perivascular inflammation in PH lungs was found, the extent of this inflammation correlated with arterial wall thickness (Stacher et al. Am J Respir Crit Care Med 2012).

In addition, the focus was put on left-heart disease which is the main cause for pulmonary hypertension in industrial countries. To date, the involvement of veins has not been elucidated. Histologically, it is difficult to identify veins. Thus, this work aimed on the identification of molelucar markers specifically expressed in veins. In order to do so, pulmonary veins of mice and rats were filled with fluorescent beads and separated with laser-microdissection from arteries. Arteries and veins were then examined by means of RT2- PCR array. Veins mainly show Ephrin B4 Receptor (EphB4) und Urokinase Plasminogen Activator Receptor (uPAR). Next, the aorta of juvenile rats was partially occluded, followed by an invasive haemodynamic monitoring 9 weeks thereafter. These animals showed, in comparison to controls, PH with left heart dysfunction. The veins were identified with retrograd instillation as described above, and then veins and arteries were described by quantitative morphology which demonstrated pronounced remodelling of veins and arteries. On human samples obtained from patiens with left-heart dysfunction, the vascular remodelling of veins and the expression of uPAR could be proved (Hunt et al. Am J Physiol Lung Cell Mol Physiol 2013).

Furthermore, the VEGF-system in primary pulmonary angiosarcomas and haemangioendotheliomas was investigated. Despite the fact that in the lung the endothelial cell is by far the most frequent one, tumours derived from this cell type are extremely rare. The expression of factors of the VEGF (Vascular Endothelial Growth Factor) pathway in primary pulmonary angiosarcomas (PEAS) and primary pulmonary haemangioendotheliomas (PEHE) was examined. It could be shown that all tumours expressed at least one factor of the VEGF-pathway (such as VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGFR-2, VEGFR-3, Tie2), potentially providing a rationale for a targeted therapy (Stacher et al. Lung Cancer 2009).

Zolán Bálint: “Non-invasive diagnosis of pulmonary hypertension with computed tomography"

Our colleague Zoltán Bálint finished his habilitation thesis in 2015. He delivered his lecture on April 9th, 2015 with the title "Non-invasive diagnosis of pulmonary hypertension with computed tomography".

Photo: Univ.-Prof. Dr. Josef Smolle, Rektor of the Medical University of Graz and Zoltán Bálint. Copyright: Med Uni Graz.

Abstract of the Habilitation thesis:

To date, there are no reliable methods available to non-invasively diagnose pulmonary hypertension (PH). Especially, the identification of the early changes in the development of the disease is a difficult task. Our aim is to provide quantitative, non-invasive and reproducible techniques with minimal user intervention for the diagnosis of PH. Our hypothesis is that quantitative assessment of the pulmonary perfusion and vasculature by means of chest CT imaging can yield relevant, reliable and easily accessible information about the presence and severity of PH.

The first parameter examined was cardiac output (CO) as a relevant diagnostic and prognostic factor for PH. We have shown that CO determination with dynamic CT can reliably reproduce the results from thermodilution method during right heart catheterisation (RHC). Therefore, this non-invasive technique might provide an alternative for repeated RHC investigations in the follow-up of patients with pulmonary arterial hypertension (Pienn et al 2013 Int J Cardiovasc Im).

We showed that the bolus propagation speed in the pulmonary artery determined by dynamic CT could discriminate between patients with and without PH and correlated with the mean pulmonary artery pressure determined by RHC. The simple determination of the propagation time and the overall low radiation dose for the examination may make this method suitable for routine clinical practice (Pienn et al 2013 Eur Radiol). The method is patented under AT 512393/2013, US 2015/0206303 and EU 2867856/2015.

We developed an automatic algorithm for lung vessel identification and extraction from the contrast-enhanced CT images of the thorax. The extracted lung vessel trees were characterised according to morphological parameters. We concluded that non-invasive quantification of pulmonary vessel tortuosity may provide a tool to evaluate PH severity (Helmberger et al 2014 PLoS One).

The development of a user interface for clinical application combining all the above listed parameters is ongoing. With the aforementioned, newly developed non-invasive protocols, data from pulmonary hypertension or other pulmonary circulation related diseases can be gathered giving the basis for the development of clinically applicable, quantitative software to diagnose lung diseases.

Grazyna Kwapiszewska: „Mechanisms of vascular remodelling in pulmonary hypertension“

Our colleague Grazyna Kwapiszewska had her habilitation lecture on June 3rd, 2015 entitled „Mechanisms of vascular remodelling in pulmonary hypertension“.

Photo: Univ.-Prof. Dr. Josef Smolle, Rektor of the Medical University of Graz and Grazyna Kwapiszewska. Copyright: Med Uni Graz.

Abstract of the Habilitation thesis:

Pulmonary hypertension (PH) is a life-threatening disease characterised by a distinct and persistent elevation of pulmonary arterial pressure. PH manifests itself in various diseases including chronic obstructive lung disease and interstitial lung fibrosis, but also rare idiopathic and familial forms exist. PH has a multifactorial pathogenesis, with both vasoconstriction and structural remodelling of the pulmonary vessels contributing to disease progression. Structural changes underlying the remodelling process include endothelial injury, abnormal migration and proliferation of smooth muscle cells (SMC) and increased extracellular matrix deposition (ECM). Changes in the expression of growth factors or their receptors have been shown to influence the development of PH. We have identified several receptors exemplarily: Protease-activated Receptor 2 (Kwapiszewska et al. Cir Res 2012), Neurotrophic Tyrosine Kinase Receptor 2 (Kwapiszewska et al. Am J Patho 2012), and Neuropeptide Y Receptor Y1 (Crnkovic et al. Br J Pharmacology 2014), whose expression was

perturbed not only in animal models of PH but also in pulmonary arteries of idiopathic pulmonary arterial hypertension patients. We have also demonstrated that all of these receptors were expressed by pulmonary arterial smooth muscle cells (PASMC), which are overrepresented in remodelled vessels. Moreover, activation of these receptors by their respective ligands led to PASMC proliferation, a hallmark of vascular remodelling. In depth in vitro and in vivo analysis led us to delineate the intracellular signalling which resulted in exacerbated ECM deposition. Pharmacological intervention with these pathways may serve as new therapeutic targets.

1.7. Translational Platform of the LBI for Lung Vascular Research

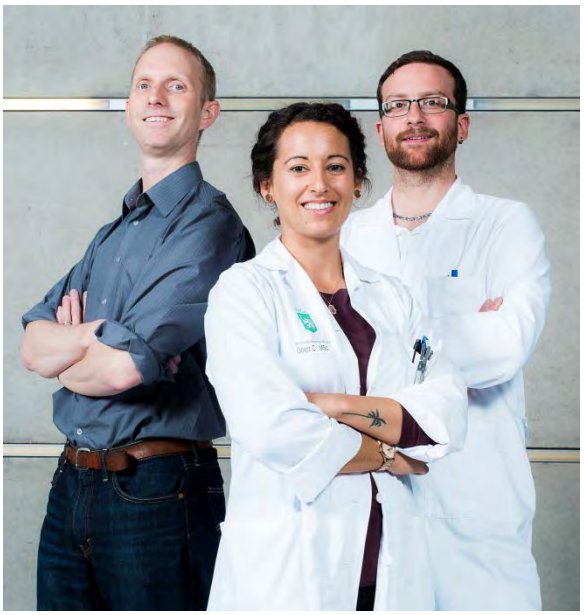


Photo (left > right): Leigh Marsh, Leader of the Translational Platform, Camilla Götz, Thomas Fuchs (Copyright: LBI-LVR)

The Translational Platform bridges the gap between the basic and clinical arms of the LBI for Lung Vascular Research. Pre-clinical models of lung diseases enable the investigation of molecules in vivo and how specific genes contribute to disease pathogenesis.

To better understand the pathogenesis of lung diseases, the Translation Platform provides a number of diverse analysis techniques to both internal and external collaborators.

Analysis of inflammatory cell populations is performed by flow cytometry; quantification of tissue remodelling utilises whole slide tissue scanning in combination with immunohistochemistry or immunofluorescence staining, tissue slides are analysed by tailored image analysis protocols. Physiological changes in the cardio-pulmonary system can be measured in vivo and ex vivo by haemodynamics, echocardiography and lung function measurements.

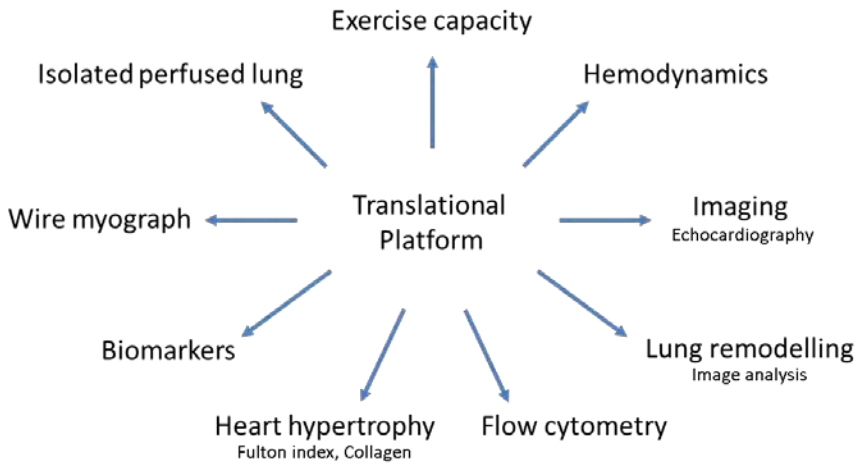


Figure 1. Summary of analysis techniques available in the translation platform.

Together with the programme line “Pathomechanisms of Pulmonary Vascular Remodelling” we were able to characterise a model of pressure overload-induced right ventricle (RV) hypertrophy. To date, the pathologic mechanisms underlying development and progression of RV diastolic dysfunction are poorly characterised and the diagnostic tools are not well established. Here, we have utilised a combination of echocardiography, haemodynamic measurements, gene expression, and morphologic analyses to characterise diastolic RV function. Our findings provide parameters that best reflect diastolic RV function and could be translated into clinicial practice to better understand RV of PH patients.

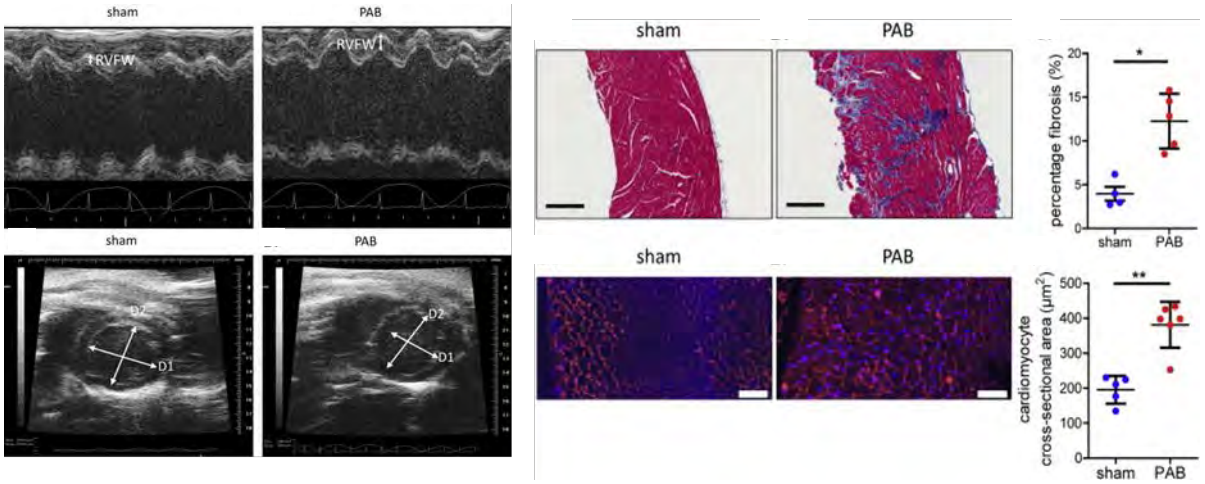


Figure 2. Pathologic changes in the heart induced by chronic pressure overload. Left panels echocardiographic characterisation; middle and right panels, image analysis to quantify fibrosis and cardiomyocyte hypertrophy. Egemnazarov B. et al., J Am Soc Echocardiogr. 2015 Jul;28(7):828-43.

Research cooperations

GRUNIG Gabriele Dr., New York University School of Medicine, Tuxedo, US

AKOS Heinemann Prof., Medical University of Graz, Austria

STROBL Herbert Prof., Medical University of Graz, Austria

SLEZAK Paul Dr., LBI for Experimental and Clinical Traumatology, Vienna, Austria

Leigh Marsh is a participant and substitute member of the management committee for Austria for the COST Action: BM1201 Developmental Origins of Chronic Lung Disease (http://www.cost.eu/about_cost)

1.8. Highlights 2015

Successful grant applications in 2015

Together with our partners, we achieved 2015 a total of four research grants, three financed by the FWF and one by the Austrian National Bank (ÖNB). Worth mentioning: Two other ÖNG grants had been already received by our colleagues Grazyna Kwapiszewska and Gabor Kovacs in the end of 2014.

Our colleague **Grazyna Kwapiszewska** received a FWF grant by the so-called Kuratoriumssitzung on March 2nd, 2015. Her project is going to investigate "The Role of transcription factor Fra-2 in pulmonary hypertension" (project 27848). The project will be running until the end of July 2018 with a total budget of EUR 326.300.-

Photo: Grazyna Kwapiszewska working in the LBI-LVR laboratory. Copyright: LBI-LVR/ Bergmann

Katharina Leithner is the leader of the project „PCK2 in lung tumours: its role for metabolism and growth". The Kuratoriumssitzung made its positive decision on November 30th, 2015 (project 28692). The project has been already started in the beginning of February 2016 and will last three years. With a budget of EUR 203.551.-, Katharina Leithner was able to set up her own independent working group!

Andrea Olschewski, as a Professor of the Experimental Anaesthesiology at the MUG, received a grant of the FWF Graduate School (DK-MOLIN) which is an educational programme at the Medical University of Graz, based on equal financial support by the 'Doktoratskolleg' (DK) scheme of the Austrian Science Fund (FWF) and the MUG. MOLIN offers a multidisciplinary graduate training programme that scrutinises the molecular and cellular mechanisms involved in the pathogenesis of inflammatory diseases, the pathogenic role of inflammation in diseases, and novel therapeutic targets to modulate inflammation using a wide range of state-of-the-art techniques (http://www.medunigraz.at/DK-MOLIN/aboutus.html).

Furthermore, **Andrea Olschewski** received an ÖNB-project (project number 16682) on December 15th, 2015 entitled "Ion channels in IPAH: possible new therapeutic options?". Based on the preliminary data gained in the LBI-LVR, a clinical proof-of-concept study will prove the impact of the inhibition of calcium-sensitive chloride channels in IPAH.

1st Poster Award at the PH-DACH Symposium 2015

November 12-14th, Heidelberg, Germany. **Grazyna Kwapiszewska**, **Anna Gungl, Valentina Biasin**, **Slaven Crnkovic**, **Leigh Marsh**, and **Andrea Olschewski** participated in the poster award competition of the PH-DACH Fall/Winter-Symposium and achieved the remarkable first place!

Photo (left > right): PD Dr. Andreas Meyer (poster jury), Prof. Dr. Ekkehard Grünig (chair PH DACH), Johanna Ohnesorge (2nd poster award, University Heidelberg), Julia Hoffmann (1st poster award, LBI-LVR Graz), and Andrea Olschewski (1st poster award, LBI-LVR Graz). Copyright: PH-DACH

Photo: Participants of the PH-DACH Symposium 2015. Copyright: PH-DACH

ÖGP-Meeting in Graz: Three Awards for our Institute!

Photos: Christian Payer during his oral presentation (photo top left). Anna Gungl receives her award by OEGP Secretary Gerneral Prim.-Doz. Dr. Bernd Lamprecht (left) and OEGP Past-President Prim. Univ. Prof. Dr. Michael Studnicka (right) (photo top right). Valentina Biasin with OEGP President Prim. Univ. Prof. Dr. Meinhard Kneussl (left) and Prof. Studnicka (right) (photo bottom left). Our LBI-participants (photo bottom right); Copyright: Österreichische Gesellschaft für Pneumologie.

Graz, 15th-17th October, 2015. Three of our colleagues were honored with awards:

- Valentina Biasin: Michael Neumann Gedächtnispreis 2015
- Christian Payer: 2nd Place of the Scientific Poster Award for Basic Research
- Anna Gungl: ÖGP Short Term Fellowship

The Michael Neumann Gedächtnispreis 2015 was given to **Valentina Biasin** for her work about "Meprin ß, a novel mediator of vascular remodelling underlying pulmonary hypertension" published in the Journal of Pathology in May 2014. This study identified a novel protease, meprin ß, which was found to be involved in collagen deposition and vascular remodelling. Due to its upregulation it influenced the smooth muscle cell proliferation.

Christian Payer reached the 2nd Place of the Scientific Poster Award for Basic Research with his abstract entitled: "Regional differences in lung vessel morphology from thoracic CT images". For him, this honor is a perfect finalisation of his diploma thesis. Christian: "It was a great experience to present my results and have the opportunity to discuss my work with the members of the ÖGP."

Anna Gungl is going to use her ÖGP Short Term Fellowship to go to the laboratory of Prof. Dr. Martin Witzenrath, Department of Infectious Diseases and Respiratory Medicine at the Charité-Universitätsmedizin in Berlin, Germany in order to learn new methods for her PhD thesis work.

18th PH Patient and Relatives Meeting-

Progress in the Treatment of Pulmonary Hypertension

Frankfurt am Main, Germany: 23rd - 25th October 2015. The "18th Patient and Relatives Meeting" for patients with pulmonary hypertension (PH) attracted many participants, who listened to the lecture of **Horst Olschewski**, Head of the Division of Pulmonology at the Hospital Graz, Austria about "Future Therapy of PAH". Horst Olschewski explained the importance of an initial combination therapy. Thus, immediately after the diagnosis the treatment is started using two or even more agents. Further studies will focus on the relationship between drug effects and side effects and investigate how humans with different gene variants and disease symptoms respond to the new drug combinations.

In a workshop, **Andrea Olschewski** discussed about the „Reasons of lung vessel remodelling“ and **Julia Hoffmann** talked about „Pulmonary hypertension: A phenomenon underlying different molecularbiological mechanisms“. Julia Hoffmann was deeply impressed by the active discussion of the participating patients: „It is a challenging but important task to explain our research directly to the patients.“

More information about this hot topic you can find here (in German): https://www.phev.de/

Photos: Chairman Mr. Hans-Dieter Kulla of the self-help organisation phev (photo top left), plenum (photo top right); podium (photo bottom left), Andrea Olschewski (photo bottom right). Copyright Thomas Füßler.

Management Workshop of the Ludwig Boltzmann Society

The Ludwig Boltzmann Society (LBG) offers annual management workshops for the directors and deputy directors of its institutes (LBI) in order to support them in team development, employee guidance as well as general management aspects. This year, the workshop, that took place in the hotel Pfeffel in the Austrian town Dürnstein between 28th and 30th September 2015, has been organised and moderated by Dr. Michael Vogler (http://www.kultur-design.at/) and Claudia Röschl (http://www.roeschl.com/). The central issue was corporate culture. Among others, the following questions were answered: How can we actively introduce LBG culture, in particular with regard to our commonality? What are the next necessary steps for a successful implementation? Our institute was represented by **Andrea Olschewski** and **Grazyna Kwapiszewska**.

Photo (left > right): Dr. Brigitte Piso (LBI HTA), Assoc. Prof. Dr. Florian Schaffenrath (LBI Neulatein), Dr. Immo Trinks (LBI ArchPro), Prof. Dr. Heinz Redl (LBI Trauma), Mag. Claudia Lingner (LBG GmbH), and Mag. Dr. Reingard Riener-Hofer (LBI CFI). Copyright: Copyright: LBI-LVR

Best oral presentation award at the MIUA conference

The Medical Image Understanding and Analysis Conference (MIUA) 2015 took place at the University of Lincoln, Lincolnshire, UK from 15th to 17th July 2015. MIUA is a UK-based meeting for the communication of research related to image analysis and its application to medical imaging and biomedicine. The conference provides an opportunity to present and discuss research in medical image understanding and analysis, which is a rapidly growing subject with ever increasing real-world applicability. There, **Michael Pienn** presented his work about "Increased tortuosity of pulmonary arteries in patients with pulmonary hypertension in the arteries" and won the best oral presentation award!

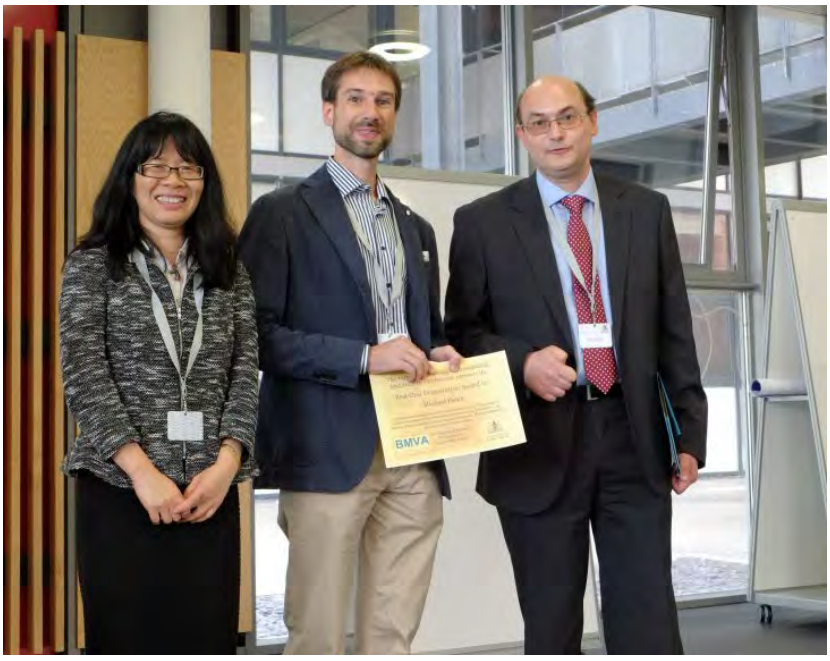
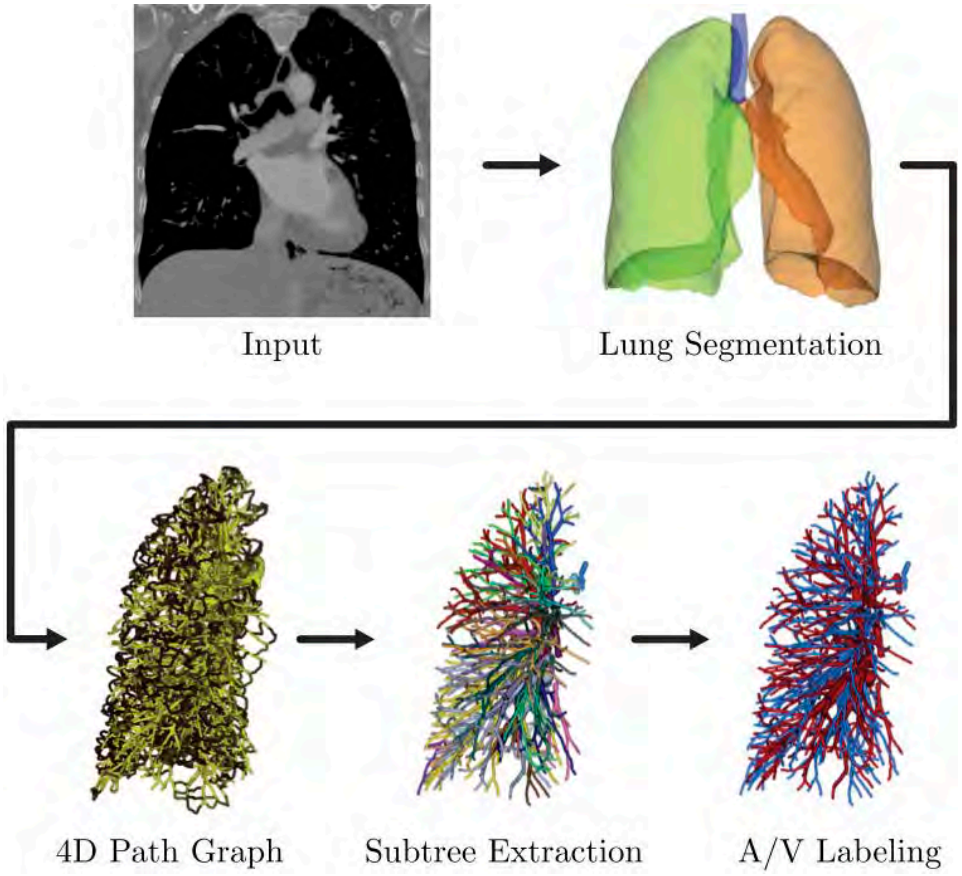


Photo (left > right): Dr. Xujiong Ye, University of Lincoln; Michael Pienn, LBI-LVR; and Dr. Tryphon Lambrou, University of Lincoln at the price award ceremony. Copyright: Courtesy of MIUA 2015.

Separation of arteries and veins in pulmonary CT images to support lung disease detection

Christian Payer successfully finished his Master thesis on on May 28th 2015. The goal of his work was to separate and analyse arteries and veins in thoracic computed tomography images. The proposed algorithm performs this task without manual intervention and is based on two integer programmes. The results of the algorithm can be used to compare the morphology of arteries and veins. This information can support physicians to be able to perform an early diagnosis of lung diseases.



This is the flow chart of the proposed algorithm. The algorithm uses thoracic contrast-enhanced CT images as input. A lung segmentation is created and the A/V separation pipeline consisting of three steps, namely the 4D path graph, the subtree extraction, and the final A/V labelling, is applied to both sides of the lung, independently.

Furthermore, Christian Payer, former member in the LBI-LVR working group of Zoltán Bálint, was proposed as one of nine applicants for the best publication at the MICCAI conference (www.miccai2015.org) in October 2015.

Task-Force Meeting of the European Respiratory Society

The European Respiratory Society supported the formation of a task force on pulmonary exercise haemodynamics. The first meeting to discuss this topic was organised by **Gabor Kovacs** who invited Prof. Philippe Hervé of the Physiology Department, University Paris Sud, Faculté de Médecine-EA4533-APHP, Le Kremlin Bicêtre, France to the LBI-LVR on April 24th, 2015. The task force has been suggested by researchers of the LBI-LVR and will be led by **Horst Olschewski** as well as by Prof. Hervé. The duty of this task force is to prepare an expert statement on pulmonary exercise haemodynamics. About 20 international experts of the field are involved including leading scientists like the editor of ERJ Prof. Marc Humbert (Director of INSERM U999, University Paris-Sud and Vice Chairman of the National Reference Centre for Pulmonary Hypertension at the Department of Respiratory and Intensive Care Medicine Hospital), Antoine Béclère (Clamart, France), the section editor of ERJ Prof. Anton Vonk-Noordegraaf (University Medical Centre, Amsterdam, the Netherlands), and Prof. Robert Naeije (Free University of Brussels, Brussels, Belgium) who participated in the Symposium on Cardiac and Vascular Stiffness in Schloss Seggau, Austria in 2014 organised by the LBI-LVR. At this task force meeting, the major duties were decided by the chairs.

Photo (left > right): Olschewski, Hervé, Kovacs. Copyright: LBI-LVR/ Olschewski.

Our participation in Meet Science 2015

Our Ludwig Boltzmann Institute for Lung Vascular Research participated in “Meet Science 2015” on April 16th in the Semper Depot in Vienna joining the other research institutes and clusters of the Ludwig Boltzmann Society. There, current research activities were presented to the Austrian Research Community.

René Baumgart Research Award 2015

For the twelfth consecutive time, the René Baumgart-Research Award was announced for a scientific work in the field of pulmonary hypertension. Within the scope of the 56th Congress of the German Society for Pneumology and Respiration Medicine, Berlin this time the price was awarded to **Julia Hoffmann** as well as to Dr. Jochen Wilhelm, Justus Liebig University of Giessen, Germany on March 19th, 2015. Prof. Ralf Ewert of the University Medical Centre Greifswald, Germany made the laudation. Hans-Dieter Kulla, Chairperson of the Self-Help Association "Pulmonary Hypertension" and Anne-Christin Kopp, cousin of the name giver of the foundation, handed the price.

The René Baumgart-Foundation was founded in 2001 by the Self-Help Association "Pulmonary Hypertension". Since 2004, each year a scientific award has been announced. The René Baumgart-Foundation supports clinical research about pulmonary hypertension in adults and children. The aim of the foundation is to gain new knowledge about pulmonary hypertension in order to enable an early diagnosis as well as new long-term therapy options that reduce the complaints of the patients and finally cure the disease.

The name giver of the René Baumgart-Foundation was born in Aalen in 1971. His mum died due to idiopathic pulmonary arterial hypertension (IPAH) when René was 10 years old. René got his diagnosis of IPAH when he was 19 years old. Before he was able to finish his education as a print worker and could perform the mastership examination. Due to the disease, he died at the age of 23. This is an informationen of the René Baumgart-Foundation.

In the excellent study of Julia Hoffmann and Dr. Wilhelm, it is proved that there are - in spite of similar rebuilding processes of the lung vessels of patients with chronic obstructive lung disease (COPD) and idiopathic pulmonary fibrosis (IPF) with pulmonary hypertension - significant differences in the genetic expression pattern of the lung arteries which influence the retinol metabolism and the signal pathways via the extra-cellular matrix. Using this knowledge, specific therapies could be developed for pulmonary hypertension patients with COPD and IPF.

Photo (left > right): Anne Kopp, Julia Hoffmann, Dr. Jochen Wilhelm, Prof. Ralf Ewert, Hans-Dieter Kulla. Copyright: René Baumgart-Foundation.

We are proud of our colleague Julia Hoffmann who graduated in Biology in 2006 at the University Lake Constance and started her thesis - supervised by Dr. Wolfgang Kübler - in Berlin, Germany at the Institute of Physiology of the Charité. In 2012, she continued her scientific work about pulmonary hypertension as a Post-Doc in the research group of Grazyna Kwapiszewska at our Ludwig Boltzmann Institute for Lung Vascular Research in Graz, Austria.

PH UP2DATE Awards 2015

Valentina Biasin and Slaven Crnkovic both won the PH UP2DATE award 2015. Each year, 3 PH UP2DATE awards are granted to young scientists for basic research in the pulmonary hypertenison field which took place this year on March 13th in Munich, Germany.

"The topic of my poster was the identification of a novel protease, meprin ß, involved in remodelling of the vessel wall. Meprin ß regulates the collagen maturation and therefore, the collagen deposition in the vessel wall. Moreover, meprin ß also modulates the smooth muscle cells proliferation." explains **Valentina Biasin**. And further: "The clinical relevance of our findings was confirmed in human patients. Here, the meprin ß expression is elevated which was published for the first time in the Journal of Pathology in 2014."

Slaven Crnkovic received the UP2DATE award for his work "NPY/Y_1receptor-mediated vasoconstrictory and proliferative effects in pulmonary hypertension" published in the British Journal of Pharmacology in 2014. He found out that, on a functional level, neuropeptide Y (NPY) acutely increased intracellular calcium levels and enhanced vasoconstriction of lung vessels preconstricted with adrenaline. Furthermore, NPY stimulated proliferation of human pulmonary arterial smooth muscle cells and activated p38 and PKD pathways. Correspondingly, higher phosphorylation of PKD was observed in remodelled vessels from PH patients. The selective Y_1 receptor antagonist, BIBO 3304, concentration-dependently inhibited vasoconstrictive and proliferative effects of NPY. "We conclude that NPY and Y_1 receptor are possible mediators of both vasoconstriction and pulmonary vascular remodelling in PH." says Slaven Crnkovic.

Photos: Prof. Ralph Schermuly (right), UKGM Giessen and Dr. Yorn Schmidt (in the middle), AOP Orphan Pharmaceuticals AG, Germany awarded the PH2UPDATE prices to our colleagues Valentina Biasin and Slaven Crnkovic. Copyright: Pfizer.

Forschungswerkstatt Berlin: Two Poster Awards for our Institute!

Rita Papp and **Bakytbek Egemnazarov** both won the 2nd poster award in the category preclinical research of the meeting „4. Forschungswerkstatt - Pulmonary Hypertension". The meeting, organised by Bayer Vital and under the scientific leadership of Prof. Werner Seeger, took place on February 27th and 28th, 2015 in Berlin.

The poster of Rita Papp is entitled "Increased expression of TMEM16A may lead to depolarisation of human pulmonary arterial smooth muscle cells in IPAH". Bakytbek Egemnazarov presented the topic "COMP as a possible negative regulator of TGF-beta signalling. Role in the right ventricular fibrosis." Bakytbek Egemnazarov is proud that his work is not only recognised but also honoured by the scientific community. His comment: "It is a good feeling to have such a positive feedback."

Photo: Awardees of the meeting. Third from the left: Bakytbek Egemnazarov. Pictured fourth from left: Rita Papp. Copyright: F. Höhler.

In the excellent study of Julia Hoffmann and Dr. Wilhelm, it is proved that there are - in spite of similar rebuilding processes of the lung vessels of patients with chronic obstructive lung disease (COPD) and idiopathic pulmonary fibrosis (IPF) with pulmonary hypertension - significant differences in the genetic expression pattern of the lung arteries which influence the retinol metabolism and the signal pathways via the extra-cellular matrix. Using this knowledge, specific therapies could be developed for pulmonary hypertension patients with COPD and IPF.

1.9. Mini-Symposium: “Pulmonary Hypertension – A Challenge”

The Ludwig Boltzmann Institute of Lung Vascular Research organised a mini-symposium about pulmonary hypertension in the frame of the official opening ceremony of the new LBI premises in the Pulmonology Building of the Medical University of Graz. On 15th January 2015, **Andrea Olschewski** introduced the participants into the history of the institute. Special talks about the challenges of pulmonary hypertension were offered by **Horst Olschewski** and **Gabor Kovacs**. Special guest of the LBG was Dr. Peter Mayerhofer. Prof. DDr. Irmgard Theresia Lippe represented the Medical University of Graz.

Photo: The participants of the mini-symposium. Copyright: LBI-LVR/ Kleinschek

Photos: Andrea Olschewski and Gabor Kovacs during their presentations. Copyright: LBI-LVR/ Kleinschek

The official invitation of the event (inGerman).

1.10. Research made in Austria

Interview with Julia Hoffmann

Julia Hoffmann started her work in the LBI-LVR in March 2012. Her focus is the examination of the signal pathways via microarrays in order to explain lung vessel remodelling e.g. in humans with pulmonary hypertension. Worth mentioning that Julia Hoffmann received three research awards during her time working in our institute: the Takeda ATS Travel Award in 2014, the 1st Place of the Scientific Poster Award for Basic Research at the ÖGP-Meeting in 2014 and the René Baumgart-Research Award in 2015.

Why did you apply for a Post-Doc position in the LBI for Lung Vascular Research in 2012? What experiences were necessary to get this job? What expectations did you have?

After 6 years in Berlin in the lab of Prof. W.M.Kübler, I was looking for a challenging new adventure in research, possibly outside of Germany. As I had already worked in the very interesting field of pulmonary hypertension, I had no problem adapting to the new tasks and projects. Still, many methods were new for me which offered the possibility to develop my skills further.

What is the focus of your work? What is the main outcome?

The focus of my work was the research on pulmonary vascular remodelling in different groups of pulmonary hypertension with a focus on human lung tissue and pulmonary arteries. Genomic, proteomic and structural analyses were performed and published in well recognised international journals.

Thinking about your work in the LBI for Lung Vascular Research within the last three years, what makes you particularly proud of? What was most challenging? What was the most impressive situation for you?

I was able to work for four years in a fantastic team with highly motivated and motivating people. I felt supported and was allowed to develop in the direction that suited my organised and structured personality. I am proud to have contributed to the success that the LBI by reliably doing my work. As in any team consisting of ambitious researchers, it was sometimes challenging to accomplish my goals and meet my personal needs. It was

impressive to see how projects and higher-level aims were realised up to now and how a scientific focus has developed within the institute.

What kind of potential do you see in your research work? Have your expectations been fulfilled? Is there anything you would you do in a different way?

I believe that my research and the results gained form part of the big picture in deciphering mechanisms underlying pulmonary vascular remodelling. My expectations were fulfilled.

What are your plans for the future? Why do you want to leave the LBI for Lung Vascular Research now?

I will start working at the DZHK (German Centre for Cardiovascular Research) beginning 01.04.2016 in order to develop new and long term perspectives for myself in research coordination and organisation. After a total of 10 years in PH science including 4 years at the LBI-LVR as a Post-Doc I believe it is time to strive for new goals.

Whom would you recommend our institute?

I recommend the LBI for Lung Vascular Research to ambitious, creative and motivated people interested in translational lung research.

Interview with Rita Papp

Rita Papp has been working as a young researcher in the LBI-LVR since 2012 and has rewarded twice during this period. In this interview, she talks about the LBI-LVR in general and her research in particular.

Rita, what is the focus of your work? What is the main outcome?

We investigate the role of ion channels in lung vascular diseases. The lung vessels transport the blood of the body on a minute by minute basis through the human lung. Ion channels are small protein structures in the cell membrane which are responsible for the permeability of the ions. Our investigations demonstrate a change in the occurrence of the chloride channel in patients with severe pulmonary vascular diseases compared to healthy individuals. This change can lead to a narrowing and to a contraction of the lung vessels and consecutively to pulmonary hypertension, a life-threatening disease. Thus, we focus on the

signalling pathways involved in these processes and could prove that blocking the chloride channels leads to a reset to normal state. These research results are an essential basis for the development of novel therapies against pulmonary hypertension.

How imortant are research awards for you?

I'm very happy about research awards because they honour our research and confirm that our results are indeed important and useful for other human beings.

What kind of potential do you see in your research work?

The most servere type of lung vascular diseases is pulmonary hypertension (PH). PH is a malicious illness because extrinsic symptoms are missing and a diagnosis is extremely difficult. Therefore, long-term therapy outcome is usually unsatisfactory. Besides, an approved therapy is available for only less than half of the affected patients. In case of younger patients, lung transplantation can be an option. Our research results can contribute to the understanding of the mechanisms which are responsible for the development of pulmonary hypertension and thus, provide the basis for an approach of novel therapies against this disease giving hope to all affected patients.

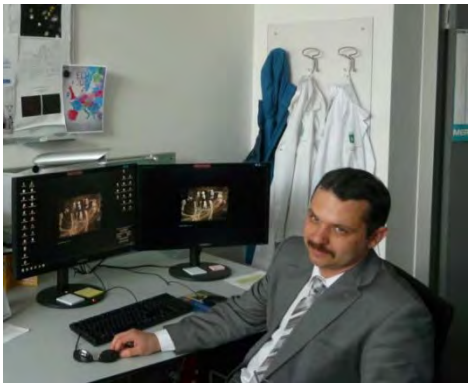
What do you wish the LBI for Lung Vascular Research for the future?

For the future, I wish our Ludwig Boltzmann Institute for Lung Vascular Research that its great success in its research about lung vascular diseases is to be continued. Most importantly, I do hope that its research leads to an early diagnosis and a better therapy of pulmonary hypertension as well as of other diseases of the lung.

What makes it so special to work in your institute?

The fascinating part for me is the intense and specific collaboration between clinical specialists on one side and basic researchers on the other side. Our interdisciplinary team works together on our research projects and so our institute operates as a catalyst to fill the gap between preclinical cutting-edge research and clinical medicine.

Interview with Zoltán Bálint



Zoltán Bálint joined the LBI-LVR in 2010 as group leader of the research group “Non-invasive Diagnostics of Pulmonary Hypertension”. His research focus is the development of a quantitative, non-invasive and reproducible technique for the assessment of the pulmonary circulation. For his research endeavors, he was honoured with the inventum 2013 price of the Austrian Patent Office in 2014. He habilitated in 2015 in Medical Physics and Biophysics at the Medical University of Graz.

Why did you apply for the position of a research group leader in the LBI for Lung Vascular Research in 2010? What experiences are necessary to make this job? What expectations did you have?

The position of a research group leader was a big, challenging step in my carrier which was worth striving for. I had already experience in scientific development, project planning and in leading research projects, but leading a research group presented a great change and required additional effort from my side, especially concerning the optimisation of time- and self-management. Further, an interesting aspect in this position was the need to change the mentality as being in the "sandwich position" between the director and the group members. I expected some difficulties at the beginning that were mostly solved by time and by the gathered experience.

What is the focus of your work? What is the main outcome?

The focus of the “Non-invasive Diagnostics of Pulmonary Hypertension” research group of the LBI-LVR is computer-aided diagnosis of lung diseases in order to facilitate early recognition of the diseases. The main outcomes can be seen in several publications, theses of students, research awards and a patent (*"Methode zur nichtinvasiven Diagnose von pulmonaler Hypertonie"*. Patent File No. A 512393/15.08.2013; Patent Publication No. US 2015/0206303-A1, issue date 23rd July 2015; EU Patent 2867856 issue date 6th May 2015).

Thinking about your work in the LBI for Lung Vascular Research within the last few years, what makes you particularly proud of? What was most challenging? What was the most impressive situation for you?

I am most proud of the *inventum 2013* price of the Austrian Patent Office which we received in November 2014. In the project, which received the price, we developed a dynamic computer tomography protocol for the evaluation of patients suffering from pulmonary hypertension. We calculated the contrast material bolus propagation speed in the pulmonary artery of the patients and observed that it was correlated with the mean pulmonary artery pressure. Thus, this parameter can discriminate between patients with and without pulmonary hypertension. The easy determination of the propagation time and the comparably low dose for the examination make this measure suitable for everyday clinical practice and can provide a basis for diagnosis of PH. Since this discovery and the recognition from the Austrian Patent Office I really feel like an inventor. On the other hand, working with patients was the most challenging experience during my time in the LBI-LVR. Nevertheless, I was mostly impressed by the performance of a patient participating in a movie for our patent.

What kind of potential do you see in your research work? Have your expectations been fulfilled? Is there anything you would do in a different way?

I see several potentials in our research: computer-aided diagnosis for lung diseases, providing an imaging-based biomarker as well as early recognition of lung diseases. I feel to have invested more than 5 years with a very good outcome. Thus, I cannot recall major decisions that I would make differently. Some minor steps probably, but in general I would act similarly.

What are your plans for the future?

I want to become a university teacher and establish my own research group dealing with the development of novel imaging-based biomarkers for life threatening diseases at the Babes-Bolyai University, Faculty of Physics, Cluj-Napoca, Romania.

Whom would you recommend our institute?

I can recommend the LBI-LVR to students who want to learn about the interdisciplinary approach of medical problems and who would like to develop themselves further in a multidisciplinary research field. Another interested party could be researchers who would like to work in a stimulating environment together with molecular biologists, medical physicists, chemists and medical doctors in order to ease the diagnosis and treatment of lung diseases.

1.11. Public Relations

Our LBI for Lung Vascular Research is presented in profile for non-scientists and non-physician on our LBI-LVR website: http://lvr.lbg.ac.at/en/institute/lbi-profile

Tracking down lung diseases by finding the causes and developing novel therapies.

Since 2010 scientists at the Ludwig Boltzmann Institute for Lung Vascular Research (LBI-LVR) have been on the track of lung diseases such as the life-threatening pulmonary hypertension. Today, the LBI-LVR, an institute of the Ludwig Boltzmann Society, is among the leading international institutes in the field of lung vascular research. Not least, this can be attributed to the unique interdisciplinary cooperation between basic researchers and physicians.

Biologists, chemists, medical professionals, pharmacologists, physicists and many other scientists at the LBI-LVR investigate lung diseases within three complementary research units: molecular and pharmacologic strategies for reverse remodelling of the pulmonary circulation, non-invasive assessment of the pulmonary circulation and the establishment of a comprehensive clinical database.

The scientists at the LBI-LVR are working together on decoding lung diseases with great commitment to understand the causes and the progression of these diseases as well as to provide the basis for more precise and safer therapies which finally should lead to a better life quality of the patients.

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.

In 2015, **Horst Olschewski** and **Gabor Kovacs** participated as invited speakers in a meeting of the PH initiative for PH patients and their relatives which took place in the Austria Trend Hotel Europa in Graz on October 9th. They focussed their lectures on the benefits and risks of physical exercises for patients with PH.

School Research Day in our Institute

November 23rd, 2015. Our Ludwig Boltzmann Institute for Lung Vascular Research opened its laboratory doors for the young visitors of the 3rd Class of the Seebacher High School Graz. In company of their teachers, the students were allowed to enter the research areas of the Centre for Medical Research (ZMF) and even participated in the experiments. **Maria Schloffer**, **Simone Tischler**, **Lisa Oberreiter** and **Elizabeth Blanz** showed the teenagers how to work with the stereomicroscope and in the cell culture. The pupils enthusiastically did the pipetting and centrifugation. Especially great fun for them was the procedure to gain their own DNA from a saliva sample supervised by **Thomas Fuchs**. Finally, all participants met in the new rooms of our institute in the Division of Pulmonology, Department of Internal Medicine at the Medical University of Graz. In front of the ultrasonoscope, **Gabor Kovacs** answered all questions of our interested guests about the diagnosis of heart and lung diseases.

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 2015 is given here:

- Lunge unter Druck - Ärzte Woche *December 2015*
- Highlights der Jahrestagung der European Respiratory Society 2015 in Amsterdam - Universum Innere Medizin *September 2015*
- Lungenhochdruck rascher erkennen - Ärzte Exklusiv *September 2015*
- Borderline Pulmonary Pressure in Scleroderma Patients linked to a Pre-Pulmonary Arterial Hypertension Condition - sclerodermanews.com *June 2015*
- Beitrag über die Forschungsarbeit (Lungenkrebszellen unter Stress) von Katharina Leithner mit Bildern aus dem LBI-LVR Labor im ZMF Graz – Steiermark heute am 2.6. um 19 Uhr *June 2015*
- Erfolgreiche Spitzenforschung made in Austria - karriere MEDIZIN *May 2015*
- STIM/ORAI1-mediated Ca influx regulates enolase-1 exteriorisation – jbc,org *May 2015*
- Forschungspreis 2015 der René Baumgart-Stiftung - presented on 37(!) different websites: artikel-presse.de, bdz-presse.de, deutschland-247.de, freie-pressemitteilungen.de, gesundheit-infos-247.de, hasselwander.co.uk, inar.de, internet-news-247.de, internet-news-spion.de, internetmarketing.or.at, kredit1a.de, nachrichten.net, neue-pressemitteilungen.de, news4press.com, newsfenster.de, oesterreich-news-247.de, online-news-247.de, online-zeitung.de, onprnews.com, pr-gateway.de, pressefeuer.at, pressekat.de, pressemitteilung.co, presseportal.co.uk, presseschleuder.com, prnews24.com, weltjournal.de, berlin-architekt.org, privat-schule.de, bauaufsicht.de, karriereratgeber.de, apotheken-anzeiger.de, tourismusnews.com110, krankheitsbild.de, spreewald-nachrichten.de, mein-presseportal.de, presseanzeiger.de *April 2015*
- Forschungspreis 2015 der René Baumgart-Stiftung - fachinformationen-medizin.de *April 2015*
- Schneller zur Diagnose Lungenhochdruck - Medical Tribune 17 *April 2015*
- Neues Diagnoseverfahren für Lungenhochdruck - Aerzte Exklusiv *April 2015*
- Den Druck aus der Lunge nehmen - derstandard.at *April 2015*
- Geistesblitz: Den Druck aus der Lunge nehmen - DER STANDARD *April 2015*
- Sauerstoffmangel erzeugt resistente Lungentumorzellen - AERZTE Steiermark *March 2015*
- Pulmonal arterielle Hypertonie: rezente Studien kommentiert - klinik *March 2015*
- Sensible Reaktion auf Hypoxie - Ärztewoche *March 2015*

- Kombinationstherapie gegen resistent Tumorzellen erforscht - oe-journal.at *February 2015*
- Wie Sauerstoffmangel Lungenkrebs triggert - derstandard.at *February 2015*
- Sauerstoffmangel erzeugt resistente Lungentumorzellen - arf.at *February 2015*
- Kombinationstherapie gegen resistente Tumorzellen erforscht - lifescienceaustria.at *February 2015*
- Pulmonal-arterielle Hypertonie: rezente Studien kommentiert - Universum Innere Medizin *January 2015*

2. Research Programme 2015

The translational LBI-LVR combines experimental know-how, innovative imaging techniques and clinical background for high-yield research in an integrated approach. The research activities of the LBI-LVR are divided into three main topics:

- Pathomechanisms of pulmonary vascular remodelling
- Non-invasive assessment of the pulmonary circulation
- Clinical database and clinical studies

As the research projects of the institute are carried out on human and related tissues and also include human studies, all projects are approved by the Ethical Committee and / or by the Austrian Federal Ministry for Science and Research.

2.1. Pathomechanisms of Pulmonary Vascular Remodelling

The research activities of the group focus on the pathomechanisms of vascular remodelling and on chronic vasoconstriction as well as impaired vasodilation in pulmonary arteries. Furthermore, we are interested in the understanding of the signalling pathways that lead to lung diseases with and without significant vascular remodelling.

2.1.1. Novel Signalling Pathways contributing to the Development of human Pulmonary Hypertension

Project Leader / Key Researcher: Grazyna Kwapiszewska

Researchers:
Andrea Olschewski
Valentina Biasin
Slaven Crnkovic
Bakytbek Egemnazarov
Julia Hoffmann
Andelko Hrzenjak
Katharina Leithner, assoc. MUG
Leigh Marsh
Chandran Nagaraj
Rita Papp
Anita Sahu-Osen
Elvira Stacher-Priehse, maternity leave

Junior Researchers:
Anna Gungl, assoc. MUG
Bence Nagy
Neha Sharma, assoc. MUG

Student:
Lena Mischkulnig (until 01.10.2015)

Technicians:
Elisabeth Blanz, assoc. MUG
Verena Braunschmid
Thomas Fuchs
Christina Gleixner
Camilla Götz
Sabine Halsegger, assoc. MUG, maternity leave
Lisa Oberreiter
Sabrina Reinisch, maternity leave
Julia Schittl, maternity leave
Maria Helene Schloffer, assoc. MUG
Simone Tischler, assoc. MUG

Project Overview

The hallmark of pulmonary hypertension (PH) is vascular remodelling. Vessel remodelling is caused by endothelial cell apoptosis, proliferation of smooth muscle cells and infiltration of inflammatory cells, as well as deposition of extracellular matrix proteins. Activation of multiple growth factor receptors lead to downstream signalling resulting in the activation of transcription factors. These downstream molecules link multiple signalling pathways, alter cellular behaviour and give rise to vascular remodelling and thereby, PH.

Research Results and Future Outlook

Human Biobank: The human tissue biobank is the core of our platform. Our tissue biobank contains samples from idiopathic pulmonary arterial hypertension (IPAH), chronic obstructive pulmonary disease (COPD) and pulmonary idiopathic fibrosis (IPF) as well as donor patient lungs that serve as controls. Currently, in our biobank we have lung samples from ~240 patients. Large numbers of cryopreserved material, paraffin embedded tissue as well as isolated smooth muscle cells, adventitial fibroblasts and parenchymal fibroblasts have been collected and form the foundation of our research programme. This material serves as a basis for the investigation of pathways involved in the pathogenesis of lung diseases.

Previously, we have analysed the degree of vascular remodelling in PH associated with lung diseases such as COPD and IPF and revealed that pulmonary arteries from these patient groups displayed various degrees of vascular remodelling which was concomitant with diverse gene expressions. The most prominent differentially regulated pathways belonged to the retinol metabolism and the extracellular matrix (ECM) (Hoffmann et al. AJRCCM 2014). For this study Julia Hoffmann, together with our collaboration partner Dr. Jochen Wilhelm, was rewarded in 2015 with the highly prestigious René-Baumgard Research Reward. We have built on this work by undertaking a compartment-specific study to elucidate the expression profile of ECM components such as collagens and their processing enzymes in donor and IPAH pulmonary arteries. In this study, we segregated intima+media from the perivascular tissue of pulmonary artery profiles by laser capture microdissection. We revealed several so far unstudied collagens (especially collagen XVIII), MMPs, ADAMs as well as TIMPs as interesting new players in the pathophysiology of IPAH. These findings have been published in the Journal “American journal of physiology. Lung cellular and molecular physiology” (Hoffmann et al. Am J Physiol Lung Cell Mol Physiol 2015 May 15;308(10):L1002-13).

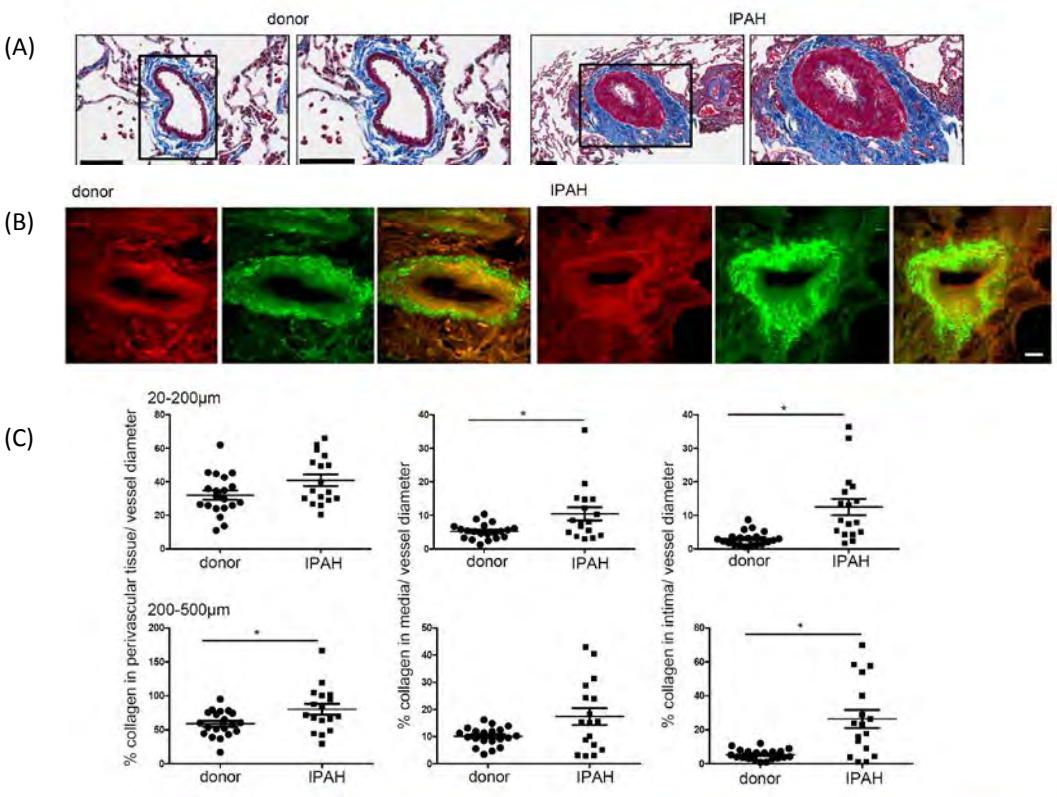


Figure 1: Collagen deposition in IPAH pulmonary arteries as shown by (A) Masson`s trichrome staining (collagen: blue), scale bar: 100µm; (B) two photon microscopy (autofluorescence signal; collagen in green: channel 495-560 nm at 1100 nm excitation; scale bar: 50 µm); (C) quantification of percentage of absolute collagen as percentage of vessel diameter in perivascular tissue, media and intima, n=20 donors and n= 17 IPAH, mean with SEM, * $p<0.05$, one dot represents 16-88 vessel profiles. (Hoffman et al. Am J Physiol Lung Cell Mol Physiol 2015 May 15;308(10):L1002-13).

Additionally, we could show that the levels of endostatin, the cleavage product of collagen XVIII, were elevated in the plasma of our IPAH patient cohort. Correlation analyses revealed that in IPAH patients, endostatin levels positively correlated with several clinically relevant parameters, including pulmonary arterial wedge pressure (PAWP), right atrial pressure (RAP), NT-proBNP, and uric acid. Significant negative correlations of endostatin levels were found with cardiac index (CI) and six minute walking distance (6MWD). Cumulatively, we have shown that endostatin might contribute to the development of IPAH and serve as a marker for disease progression (Hoffmann et al. Am J Physiol Lung Cell Mol Physiol 2015 May 15;308(10):L1002-13).

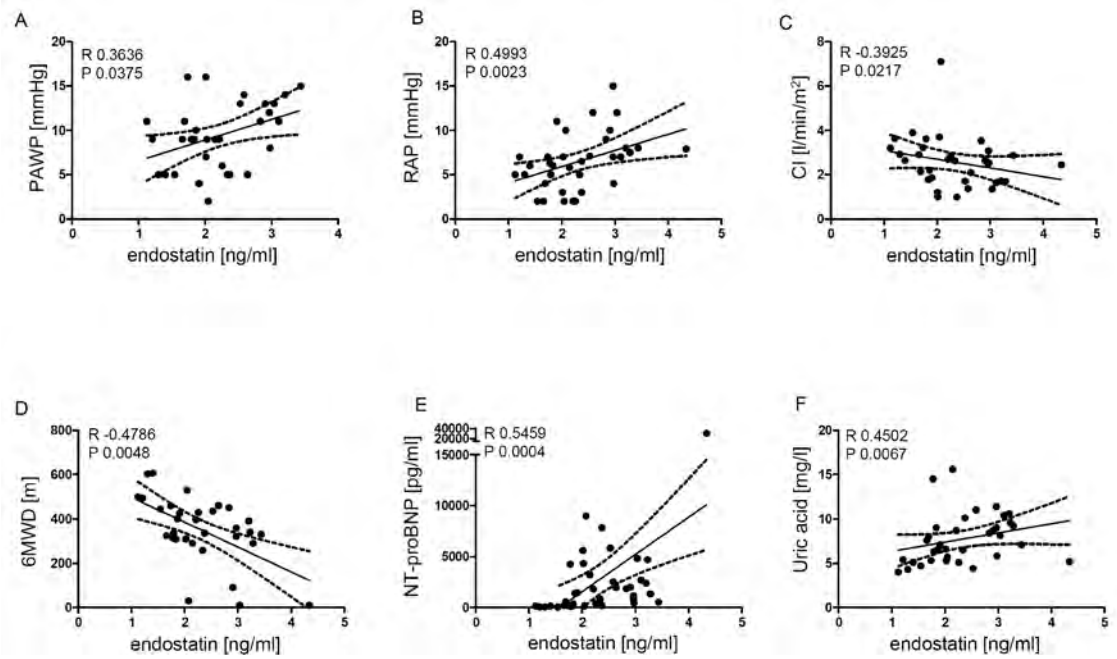


Figure 2: Significant correlation of endostatin levels with clinical parameters of IPAH patients PAWP (A), RAP (B), NT-proBNP (E) and uric acid (F) and negative correlation with CI (C) and 6MWD (D). R:Spearman R, p: significance level (Hoffmann et al. Am J Physiol Lung Cell Mol Physiol 2015 May 15;308(10):L1002-13).

Deciphering the molecular pathways that lead to vascular remodelling and PH

Working together with the translational platform, we have further elaborated on the role of AP-1 complex in vascular remodelling and could show that HMGB1 stimulated p38, extracellular signal-regulated kinase (ERK) and c-Jun N-terminal kinase (JNK) phosphorylation. Silencing of the downstream AP-1 protein, c-Jun, ablated the HMGB1-induced proliferation of pulmonary arterial smooth muscle cells (PASMC). These results led us to the conclusion that inflammatory components such as HMGB1 can contribute to PASMC proliferation and therefore, potentially to vascular remodelling and pathogenesis of PH. Importantly, increased levels of HMGB1 were observed in serum of IPAH and PH due to COPD (Zabini et al. J Cell Mol Med. 2015 May;19(5):1151-61).

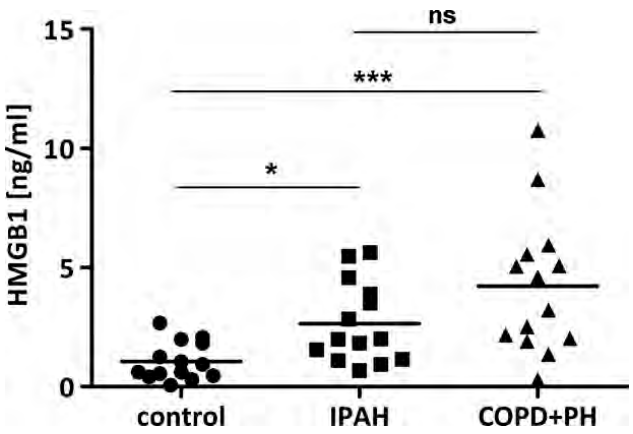


Figure 3: Increased levels of HMGB1 in serum of IPAH- and PH due to COPD patients.
*P < 0.05, ***P < 0.001, ns not significant. (Zabini et al. J Cell Mol Med. 2015 May;19(5):1151-61).

We have previously shown that another AP-1 component, Fra-2, is involved in vascular remodelling and that its overexpression leads to pulmonary hypertension (Biasin et al. J Pathol. 2014 May;233(1):7-17). For this work, Valentina Biasin was awarded with the Michael Neumann Price 2015 from the Austrian Pneumology Society. Currently, we are futher investigating the role of AP-1 components in the development of vasular remodelling. In the frame of the newly granted FWF stand alone project, the special focus will be put towards delineating the role of Fra-2 in pulmonary hypertension. We are also expanding our interest in downstream Fra-2 target genes which could be crucial for vascular remodelling. In our preliminary results, we delineated the role of Fra-2 in inflammation, lung parenchymal and vascular alterations. For these findings we have received the 1st poster award at the PH-DACH Symposium in Heidelberg. . Cumulatively, in our studies we could show the important link between transcription factors, inflammation and extracellular matrix deposition which ultimatively lead to vascular remodelling.

2.1.2. Function of Ion Channels and Regulators of Calcium Homeostasis in Pulmonary Vasculature

Group Members see 2.1.1.

Project Overview

Ion channels play an important role, both in the systemic and the pulmonary vasculature. In pulmonary vascular diseases, such as PAH, the role of different ion channels has been suggested. Based on our previous work, we focus potential implication of channels, exchangers and pumps in pulmonary vascular diseases.

Research Results and Future Outlook

The research of the group covers a wide range of studies such as the role of endothelium for the vascular integrity including inflammation, mechanisms of drug-induced pulmonary arterial hypertension, the relevance of the transporters for pulmonary vascular and right ventricle function, and ion channel distribution in pulmonary arteries in healthy controls and obtained from patients with pulmonary vascular remodelling in IPAH, COPD and IPF.

Regulation of the pulmonary vascular tone by NADPH-oxidase in lung diseases:

We currently investigate the role of NADPH oxidase (NOX) enzymes in pulmonary vascular diseases and in inflammatory lung diseases. NOX enzymes catalyse the reduction of molecular oxygen to superoxide leading to the generation of reactive oxygen species (ROS). ROS function as signalling molecules and regulators of cell function when they are generated in a compartmentalised and regulated manner. NOX enzymes play a role in the development of acute lung injury (ALI/ARDS), in pulmonary hypertension, in obstructive lung disorders and more importantly, in lung fibrosis. Here, we examine the roles of these ROS-generating enzymes in the pathogenesis of pulmonary vascular remodelling and asthma. Our findings demonstrate a crucial role of p22phox dependent NADPH oxidase for the development of mucus hypersecretion and airway hyperreactivity in a mouse model of asthma. Another study delineate the pivotal role of NADPH oxidase in the pulmonary circulation under hypoxia, showing that a functional NADPH oxidase system is important under physiological and pathological conditions, and thus might have therapeutic and diagnostic value in the human disease. The results of both investigations are currently under review.

The role of ion channels and transporters for the regulation of the pulmonary tone:

ABC transporters are active transmembrane proteins capable to move a wide variety of substrates across extra- and intracellular membranes, thereby modulating cell metabolism and cellular toxicity. Our recent study investigated the distribution of ABC transporters in IPAH. We explored the role of ABCG2 in hypoxia-induced remodelling of the right ventricle and provide evidence that under chronic hypoxia, loss of ABCG2 leads to biventricular fibrosis with diastolic dysfunction, without affecting RV afterload, capillary density or hypoxia-induced pulmonary vascular remodelling. The results of this investigation are currently under review.

The distribution and regulation of ion channels in pulmonary hypertension is still only poorly documented, and there is a compelling need for a robust validation of this observation. In addition, posttranslational modifications rather than modulation at the expressional level affect ion channel function in the pulmonary circulation. Therefore, rescuing of ion channel activity may represent an important therapeutic target for vasodilation in PH. Our research focus on the expression of the different ion channels and calcium handling proteins as well as on ion transporters at mRNA and at functional level compared with pulmonary arteries from control lungs. We are currently deciphering several molecular mechanisms underlying pulmonary vascular remodelling.

Scientific Cooperations

COGOLLUDO Angel Prof., Universidad Complutense de Madrid, Spain

EFERL Robert Dr., Medical University of Vienna, Austria

HAITCHI Hans Michael Prof., University Southampton, UK

HEINEMANN Akos Prof., Medical University of Graz, Austria

HOEFLER Gerald Prof., Medical University of Graz, Austria

KLEPETKO Walter Prof., Medical University of Vienna, Austria

KUEBLER Wolfgang Prof., St. Michael's Hospital, Toronto, Canada

SCHMIDT Albrecht Dr., Medical University of Graz, Austria

WEIR E. Kenneth Prof., University of Minneapolis, Minnesota, US

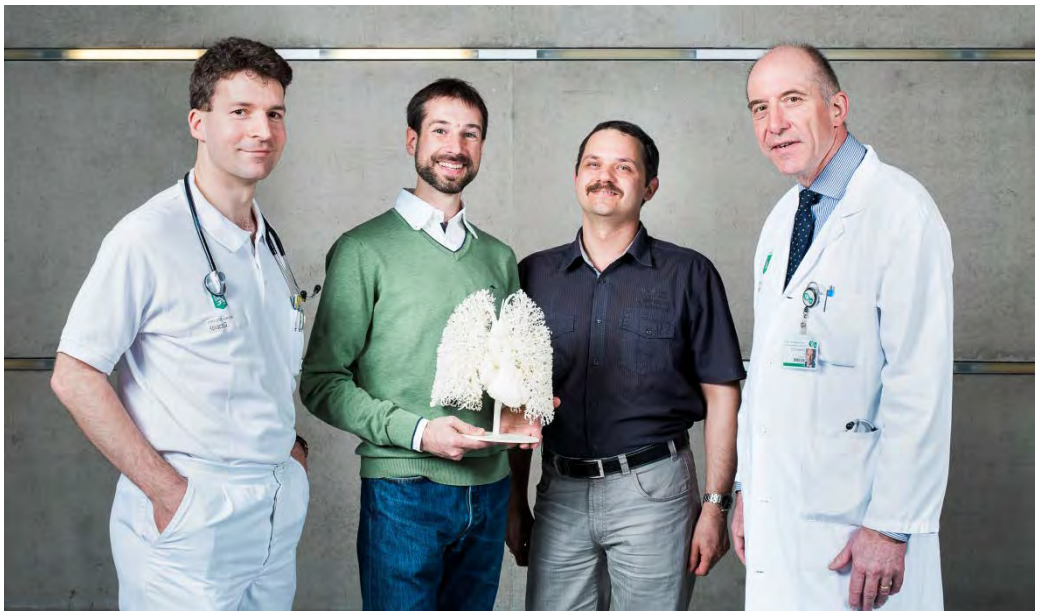
WEISSMANN Norbert Prof., ECCPS, University Giessen Lung Centre, Giessen, Germany

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. Non-invasive Diagnostics of Pulmonary Hypertension



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Project Leader / Key Researcher: Zoltán Bálint

Researcher
Horst Olschewski, Chair of the Division of Pulmonology, MUG/LKH Graz
Junior Researcher (PhD-Student)
Michael Pienn
Master Student
Christian Payer

Project Overview

One of our primary goals is to provide automatic, imaging based software for non-invasive diagnosis of pulmonary hypertension. For this purpose, we developed an automatic algorithm for lung vessel identification and classification from thoracic contrast-enhanced computed tomography (CT) images. The results of the algorithm validation were published in the Lecture Notes for Computer Science Journal. We found that arteries contribute to the increased lung vessel tortuosity in pulmonary hypertension. The results were presented by Christian Payer and Michael Pienn at conferences. The development of a user interface for clinical application combining all the quantitative readouts of the lung is ongoing.

With the software algorithms developed in this project, data from pulmonary hypertension or other pulmonary circulation related diseases can be gathered giving the LBI for Lung Vascular Research the basis for the development of clinically applicable, quantitative software to diagnose pulmonary hypertension.

Research Results and Future Outlook

In order to facilitate earlier diagnosis of lung vascular diseases, the team of Zoltán Bálint, along with colleagues from the Graz University of Technology, created a fully automated algorithm for the identification and characterisation of arteries and veins from thoracic CT images. The proposed algorithm performs the artery-vein separation without manual intervention using two optimisation functions. The performance of the automatic algorithm was compared using the manually annotated LBI for Lung Vascular Research Pilot CT Study dataset, which consists of 25 anonymised, thoracic CT scans of clinically well characterised patients, who underwent clinical examinations at the Division of Pulmonology, Medical University of Graz. The data was presented by Christian Payer at the "International Conference on Medical Image Computing and Computer Assisted Intervention - MICCAI" in Munich in October 2015. He has been awarded with the Student Bursary Award and he was nominated as one of nine "Runners Up for Student Best Paper Awards" at the MICCAI conference.

Christian Payer presented his work entitled: "Regional differences in lung vessel morphology from thoracic CT images" at the Annual Meeting of the Austrian Pneumology Society and won the 2nd Place of the Scientific Poster Award for Basic Research.

The quantitative readouts of the arterial and venous vessel trees correlated with the patients´ clinical parameters and identified pulmonary hypertension with a remarkable sensitivity and specificity. The data was presented by Michael Pienn at the Medical Image Understanding and Analysis Conference in Lincolnshire, UK. The presentation was honoured with the Best Oral Presentation Award.

Zoltán Bálint finished his habilitation thesis entitled "Non-invasive diagnosis of pulmonary hypertension with computed tomography" in April 2015 at the Medical University of Graz. Christian Payer had a successful defence of his Master thesis in May 2015 at the Graz University of Technology.

As a core facility for image acquisition and medical signal processing, we participated in projects of other research groups of our institute as well as in external projects resulting in two publications in 2015.

Currently, we are performing an in-depth analysis of our quantitative parameters of lung vessels. We will then extend our readouts for individual lung regions. In parallel, together with the Institute for Clinical Radiology of the LMU Hospital, Munich, Germany we are analysing thoracic CT images of patients suspected of pulmonary embolism who underwent CT examination but were ultimately negative for any relevant lung or heart disease. This way we can provide reference values for our readouts for healthy controls and use them as a basis for comparison.

In 2015, we initiated a cooperation with VU University Amsterdam on animal CT data acquisition and analysis. We will develop software for automatic quantitative analysis of lung vessel morphology from thoracic CTs of small animals.

The prospective, blinded validation of our previous results from dynamic acquisitions of the contrast material bolus passage through the lung vasculature is ongoing and we will reach the projected patient number by the end of 2016.

Scientific Cooperations

BOGAARD Harm-Jan, VU University Amsterdam, The Netherlands

BURGARD Caroline Dr., University Hospital Grosshadern, Ludwig Maximilians-University, Munich, Germany

BREDIES Kristian Prof., Karl-Franzens University of Graz, Austria

FUCHSJÄGER Michael Prof., Medical University of Graz, Austria

JOHNSON Thorsten PD Dr., University Hospital Grosshadern, Ludwig Maximilians-University, Munich, Germany

KULLNIG Peter Univ.-Doz. Dr., DiagnostikZentrum Graz, Austria

MEINEL Felix Dr., University Hospital Grosshadern, Ludwig Maximilians-University, Munich, Germany

ROBBEN David, iMINDS - Medical Image Computing, KU Leuven, Belgium

SLEZAK PAUL Dr., LBI Experimental and Clinical Traumatology, Vienna, Austria

SORANTIN Erich Prof., Medical University of Graz, Austria

STOLLBERGER Rudolf Prof., Graz University of Technology, Austria

URSCHLER Martin Dr., LBI for Clinic Forensic Imaging & Graz University of Technology, Austria

2.3. Clinical Database and Clinical Studies

Copyright: LBI-LVR

Project Leader / Key Researcher: Gabor Kovacs

Researchers
Horst Olschewski, Chair of the Division of Pulmonology, MUG/LKH Graz
Alexander Avian (statistician), assoc. MUG
Philipp Douschan, assoc. MUG
Bahil Ghanim, assoc. Medical University of Vienna
Balazs Odler, assoc. MUG
Susanne Pfeiffer
Adrienn Tornyos
Junior Researcher (PhD Student)
Vasile Foris
Study Nurse
Daniela Kleinschek
Student Assistant
Fabian Gruber

Project Overview

The major task of our research group is the management of an integrative clinical database of patients with pulmonary vascular diseases, mainly with pulmonary hypertension (PH) and at risk for this disease. The databank includes a biobank, in which serum and plasma samples of well characterised patients are stored. One of the main research purposes is the development and evaluation of new methods for an early and non-invasive detection of PH.

A special task of our group is the integration of physiological aspects in clinical science in the field of pulmonary haemodynamics.

Research Results and Future Outlook

Integrative Database, Biobank, Biomarkers

The establishment and maintenance of an integrative database remained one of the most important tasks of our research group. This provides easily accessible data from all patients, including complete diagnostic data at all important time points. Until now, we have included approx. 1600 patients in the database and its further extension is planned for 2016.

In 2015, we performed an analysis on the frequency of comorbidities in patients with pulmonary hypertension. We found that cardiopulmonary comorbidities are more common in patients suffering from borderline, mild and moderate stages of PH and less frequent in patients with severe pulmonary hypertension. These results may suggest that a severe pulmonary hypertension represents an isolated pulmonary vascular disease, while mild to moderate PH may be a pulmonary vascular manifestation of multi-organ disorders.

In addition, we analysed the acute haemodynamic changes of the pulmonary vasculature during pharmacologic testing and found that changes in pulmonary vascular resistance are only weakly associated with baseline haemodynamics, challenging the concept of a vasoconstrictive disease turning into a “fixed” vasculopathy with disease progression.

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. The results of the study will be presented in 2016, the initiation of a prospective study is also planned.

In 2015, the role of biomarkers in the diagnosis and prognostic evaluation of pulmonary hypertension remained in focus of our activities. As special biomarkers, the potential role and clinical relevance of endothelial progenitor cells were further investigated in patients with PH. The results were presented at international meetings. International cooperations in biomarker research were established with PAH centres in Zurich and Regensburg, Germany. As part of the clinical database, serum, plasma and full blood of patients with PH and at risk for PH are continuously being reserved in the biobank of the Medical University of Graz. The

samples of this biobank are and will be used in different studies by all research groups of the LBI-LVR.

Diagnostic approaches in PH and physiological approaches

In 2015, several larger clinical projects were continued. The prospective evaluation of MRI based haemodynamic assessment of PH patients and its comparison with other non-invasive methods was initiated in 2014 as part of an ÖNB Grant. The main objective is to compare haemodynamic variables of right heart catheterisation, MRI and echocardiography for the evaluation of patients with pulmonary hypertension. In the echocardiography arm of the study we included already over 100 patients, the number of MRI investigations is above 40. The study will be continued in 2016, the analysis and presentation of the data are expected for 2017.

The study aiming the early recognition of PH in patients with liver cirrhosis recruited successfully in 2015 and is planned to be finished at reaching 200 study patients within 2016.

The study investigating the frequency of pulmonary complications in patients with Sjögren's syndrome also recruited successfully; 45 patients were included in 2015, building one of the largest cohorts in this field. The study will be continued in 2016.

The investigation of exercise pulmonary physiology remained one of the major goals of our group. In one of our recent studies we applied the old and the suggested new definition of exercise-PH on a historical cohort of normal subjects and asked the question if the assessment of pulmonary arterial wedge pressure and pulmonary vascular resistance during exercise in addition to total pulmonary resistance might provide additional information about subjects with elevated pulmonary arterial pressure values during exercise. We found that the proposed new definition of exercise-PH decreased the rate of false positive findings in healthy subjects from 13.7% to 2.5% (Figure). The additional consideration of cardiac output and pulmonary vascular resistance during exercise may provide further information and help to distinguish patients with latent left heart disease from early pulmonary vascular disease.

Adding to physiological approaches, in 2015 we initiated a study investigating the effects of intrathoracic pressure on the pulmonary circulation in different PH groups.

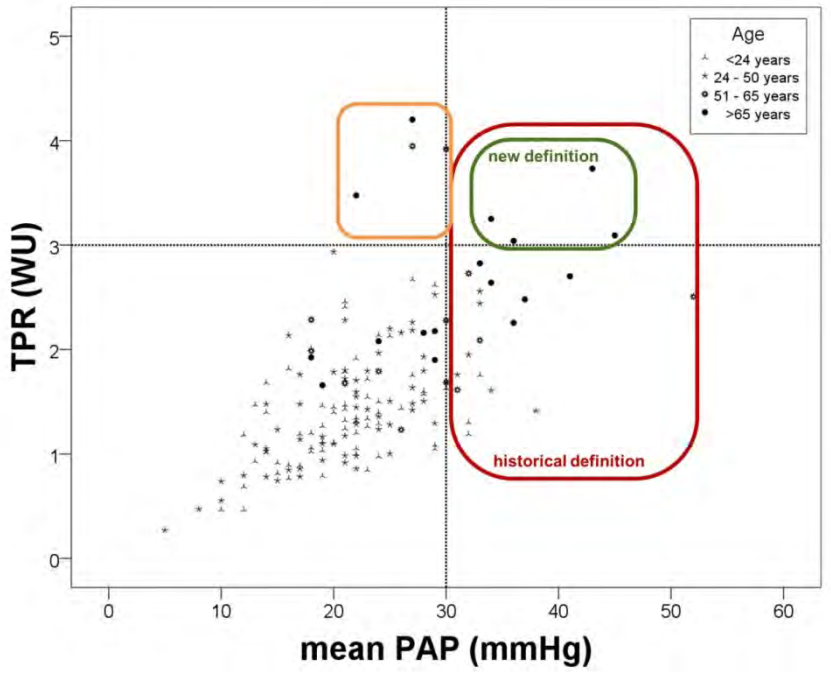


Figure: mPAP (mmHg) vs. TPR (WU) in n=160 healthy individuals at maximal exercise. The red area includes patients with exercise-PH according to the historical definition (mPAP>30mmHg), the green area includes patients with exercise-PH according to the suggested new definition (mPAP>30mmHg and TPR>3WU). The orange area represents subjects with TPR>3WU (either due to increased PVR or increased PAWP) but mPAP≤30mmHg, due to peripheral muscular limitation.

Scientific Cooperations

ABERER Elisabeth Prof., Medical University of Graz, Austria

BERGHOLD Andrea Prof., Medical University of Graz, Austria

BRODMANN Marianne Prof., Medical University of Graz, Austria

GRANINGER Winfried Prof., Medical University of Graz, Austria

HORWATH-WINTER Jutta Priv.-Doz. Dr., Medical University of Graz, Austria

LANGE Tobias Dr., University Hospital Regensburg, Germany

MAIER Robert Ass-Prof. Dr., Medical University of Graz, Austria

NINABER Maarten Dr., University Leiden Medical Centre, Leiden, Netherlands

PEACOCK Andrew Prof., University of Glasgow, Scotland, UK

RAGGAM Reinhard Dr., Medical University of Graz, Austria

ROSENKRANZ Stephan Prof., University Hospital Köln, Germany

SARGSYAN Karine Dr., Medical University of Graz, Austria

SCHLENKE Peter Prof., Medical University of Graz, Austria

SILL Heinz Prof., Medical University of Graz, Austria

STAUBER Rudolf Prof., Medical University of Graz, Austria

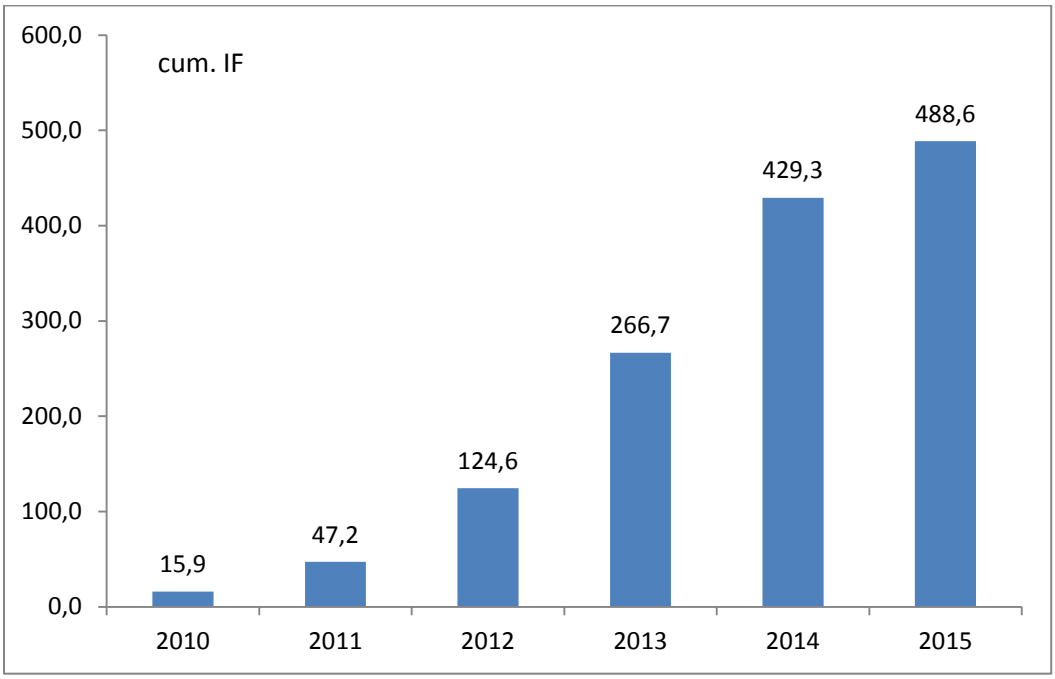
TAUBE Christian Prof., University Leiden Medical Centre, Leiden, Netherlands

TRINKER Martin Dr., Klinikum Bad Gleichenberg, Austria

ULRICH Silvia Priv.Doz., University of Zurich, Switzerland

2.4. Publications of the LBI for Lung Vascular Research 2015

Starting in 2010 when our institute was founded, the cumulative impact factor, an indicator for the quality of our scientific publications with LBI-LVR affiliation, reached the remarkable value of 488,6 at the end of the year 2015 (see graphic below).



Here, the publications of 2015 are listed:

Original scientific publications (with LBI-LVR affiliation)

Didiasova M, Zakrzewicz D, Magdolen V, Nagaraj C, Bálint Z, Rohde M, Preissner KT, Wygrecka M. STIM1/ORAI1-mediated Ca2+ influx regulates enolase-1 exteriorisation. J Biol Chem. May 2015; 290(19):11983-99. IF 4.573.

Egemnazarov B, Schmidt A, Crnkovic S, Sydykov A, Nagy BM, Kovacs G, Weissmann N, Olschewski H, Olschewski A, Kwapiszewska G, Marsh LM. Pressure overload creates right ventricular diastolic dysfunction in a mouse model: assessment by echocardiography. J Am Soc Echocardiogr. Jul 2015; 28(7):828-43. IF 4.056.

Fischer C, Leithner K, Wohlkoenig C, Quehenberger F, Bertsch A, Olschewski A, Olschewski H, Hrzenjak A. Panobinostat reduces hypoxia-induced cisplatin resistance of non-small cell lung carcinoma cells via HIF-1α destabilisation. Mol Cancer. Jan 2015; 14(1):4. IF 4.257.

Hoffmann J, Marsh LM, Pieper M, Stacher E, Ghanim B, Kovacs G, König P, Wilkens H, Haitchi HM, Hoefler G, Klepetko W, Olschewski H, Olschewski A, Kwapiszewska G. Compartment specific expression of collagens and their processing enzymes in intrapulmonary arteries of IPAH patients. Am J Physiol Lung Cell Mol Physiol. May 2015; 308(10): L1002-13. IF 4.080.

Konya V, Maric J, Jandl K, Luschnig P, Aringer I, Lanz I, Platzer W, Theiler A, Bärnthaler T, Frei R, Marsche G, Marsh LM, Olschewski A, Th Lippe I, Heinemann A, Schuligoi R. EP4 receptor prevents endotoxin-induced neutrophil infiltration into the airways and enhances microvascular barrier function. Br J Pharmacol. 2015. Jun 23. doi: 10.1111/bph.13229. IF 4.842

Kovacs G, Olschewski H. Borderline pulmonary pressures in scleroderma - a 'pre-pulmonary arterial hypertension' condition? Arthritis Res Ther. May 2015; 17(1):123. IF 3.753

Kwapiszewska G, Stacher E, Olschewski A. Physiologie, Klassifikation, Pathologie und Pathophysiologie. Das Wichtigste in aller Kürze. Pneumologe 2015; 12:373-380.

Leithner K, Hrzenjak A, Trötzmüller M, Moustafa T, Köfeler HC, Wohlkoenig C, Stacher E, Lindenmann J, Harris AL, Olschewski A, Olschewski H. PCK2 activation mediates an adaptive response to glucose depletion in lung cancer. Oncogene. Feb 2015; 34(8):1044-50. IF 8.459.

Olschewski A, Weir EK. Redox regulation of ion channels in the pulmonary circulation. Antioxid Redox Signal. Feb 2015; 22(6):465-85. IF 7.407.

Olschewski H, Kovacs G. ESC guidelines 2015 on pulmonary hypertension [article in German]. Herz. Dec 2015; 40(8):1055-60. IF 0.690.

Reimann S, Fink L, Wilhelm J, Hoffmann J, Bednorz M, Seimetz M, Dessureault I, Troesser R, Ghanim B, Klepetko W, Seeger W, Weissmann N, Kwapiszewska G. Increased S100A4 expression in the vasculature of human COPD lungs and murine model of smoke-induced emphysema. Respir Res. Oct 2015; 16: 127. doi: 10.1186/s12931-015-0284-5. IF 3.093.

Reiter G, Reiter U, Kovacs G, Olschewski H, Fuchsjäger M. Blood flow vortices along the main pulmonary artery measured with MR imaging for diagnosis of pulmonary hypertension. Radiology. Apr 2015; 275(1):71-9. IF 6.867.

Troester N, Palfner M, Schmidberger E, Olschewski H, Avian A. Sleep related breathing disorders and inflammation - the missing link? A cohort study evaluating the interaction of inflammation and sleep related breathing disorders and effects of treatment. PLoS One. Sep 2015; 10(9):e0137594. IF 3.234.

Zabini D, Crnkovic S, Xu H, Tscherner M, Ghanim B, Klepetko W, Olschewski A, Kwapiszewska G, Marsh LM. High-mobility group box-1 induces vascular remodelling processes via c-Jun activation. J Cell Mol Med. May 2015; 19(5):1151-1161. IF 4.014.

Original scientific publications (without LBI-LVR affiliation)

Hecker M, Linder T, Ott J, Walmrath HD, Lohmeyer J, Vadász I, Marsh LM, Herold S, Reichert M, Buchbinder A, Morty RE, Bausch B, Fischer T, Schulz R, Grimminger F, Witzenrath M, Barnes M, Seeger W, Mayer K. Immunomodulation by lipid emulsions in pulmonary inflammation: a randomised controlled trial. Crit Care. May 2015; 19(1):226. IF 4.476.

Naeije R, Vonk Noordegraaf A, Kovacs G. Exercise-induced pulmonary hypertension: at last! Eur. Respir. J. Sep 2015; 46(3):583-6. IF 7.636.

Olschewski H. Imatinib for pulmonary arterial hypertension - Wonder drug or killer drug? Respiration. Jun 2015; 89(6):513-4. IF 2.593.

Presentations at international conferences: oral communications

Biasin V, Wygrecka M, Gungl A, Ghanim B, Klepetko W, Marsh LM, Olschewski A, Kwapiszewska G. Role of meprin ß in lung fibrosis. Winterschool “Proteinases and Inhibitors”, Feb 2015; Tiers, Italy.

Douschan P, Kovacs G, Foris V, Olschewski A, Olschewski H. Impact of cardiopulmonary comorbidities on pulmonary haemodynamics. Pneumo Update, Jun 2015; Igls, Austria.

Foris V. Difficult cases, simple solutions. Pneumo Update, Jun 2015; Igls, Austria.

Foris V, Kovacs G, Avian A, Douschan P, Ghanim B, Klepetko W, Olschewski A, Olschewski H. Blood derived biomarkers in pulmonary arterial hypertension. 6th International Conference on Biomarkers & Clinical Research, Aug 2015; Toronto, Canada.

Kovacs G. Early pulmonary vascular disease in scleroderma. ERS Meeting, Sep 2015; Amsterdam, Netherlands.

Payer C, Pienn M, Bálint Z, Olschewski A, Olschewski H, Urschler M. Automatic artery-vein separation from thoracic CT images using integer programming. 18th International Conference on Medical Image Computing and Computer Assisted Intervention, Oct 2015; Munich, Germany.

Payer C, Pienn M, Urschler M, Kovacs G, Douschan P, Olschewski A, Olschewski H, Bálint Z. Regional differences in lung vessel morphology from thoracic CT images. Wiener Klinische Wochenschrift 2015; 127(19-20):812-812. IF 0.836. ÖGP Annual Meeting, Oct 2015; Graz, Austria.

Pienn M, Payer C, Olschewski A, Olschewski H, Urschler M, Bálint Z. Pulmonary arterial tortuosity as a non-invasive diagnostic tool for pulmonary hypertension. 13th National Conference of Biophysics, Jun 2015; Timisoara, Romania.

Pienn M, Payer C, Olschewski A, Olschewski H, Urschler M, Bálint Z. Increased tortuosity of pulmonary arteries in patients with pulmonary hypertension in the arteries. MIUA Conference, Jul 2015; Lincoln, UK.

Reiter G, Reiter U, Kovacs G, Janig C, Olschewski H, Fuchsjäger M. Magnetic resonance imaging-based diagnosis of pulmonary hypertension: 4D flow versus standard functional indices. European Congress of Radiology, Mar 2015; Vienna, Austria.

Reiter U, Reiter G, Kovacs G, Adelsmayr G, Greiser A, Olschewski H, Fuchsjäger M. Left ventricular myocardial remodelling in pulmonary hypertension: a non-contrast magnetic resonance T1 mapping study. European Congress of Radiology, Mar 2015; Vienna, Austria.

Wurm M, Pienn M, Kovacs G, Kullnig P, Olschewski A, Olschewski H, Bálint, Z. Histogram analysis of lung CT scans of pulmonary hypertension patients. International Student Congress of the Medical University of Graz (ISC), Jun 2015; Graz, Austria.

Presentations at international conferences: posters

Biasin V, Marsh LM, Egemnazarov B, Wilhelm J, Ghanim B, Klepetko W, Wygrecka M, Olschewski H, Eferl R, Olschewski A, Kwapiszewska G. Meprin-ß, novel contributor to vascular remodelling. PH UP2DATE Conference, Mar 2015; Munich, Germany.

Biasin V, Wygrecka M, Gungl A, Ghanim B, Klepetko W, Marsh LM, Olschewski A, Kwapiszewska G. Contribution of meprin ß in lung fibrosis. Pneumo Update, Jun 2015; Igls, Austria.

Biasin V, Wygrecka M, Gungl A, Ghanim B, Klepetko W, Marsh LM, Olschewski A, Kwapiszewska G. Involvement of the proteases meprins in human lung fibrosis. ÖGP Annual Meeting, Oct 2015; Graz, Austria.

Crnkovic S, Egemnazarov B, Jain P, Seay U, Gattinger N, Marsh LM, Bálint Z, Kovacs G, Ghanim B, Klepetko W, Schermuly RT, Weissmann N, Olschewski A, Kwapiszewska G. NPY/NPY1R mediated vasoconstrictory and proliferative effects in pulmonary hypertension. PH UP2DATE Conference, Mar 2015; Munich, Germany.

Douschan P, Kovacs G, Foris V, Avian A, Olschewski A, Olschewski H. Frequency of cardiopulmonary comorbidities in patients with pulmonary hypertension. ATS Conference, May 2015; Denver, US.

Douschan P, Kovacs G, Foris V, Avian A, Olschewski A, Olschewski H. Survival and cardiopulmonary comorbidities in patients with upper-normal- and borderline-PAP elevation. ÖGP Annual Meeting, Oct 2015; Graz, Austria.

Douschan P, Kovacs G, Foris V, Avian A, Olschewski A, Olschewski H. Impact of pulmonary haemodynamics and cardiopulmonary comorbidities on survival in patients at risk for PH. PH-DACH Symposium, Nov 2015; Heidelberg, Germany.

Douschan P, Kovacs G, Foris V, Olschewski A, Olschewski H. Impact of cardiopulmonary comorbidities on pulmonary haemodynamics. Pneumo Update, Jun 2015; Igls, Austria.

Douschan P, Kovacs G, Foris V, Olschewski A, Olschewski H. Cardiopulmonary comorbidities are associated with haemodynamics in pulmonary arterial hypertension. ERS Meeting, Sep 2015; Amsterdam, Netherlands.

Egemnazarov B, Crnkovic S, Olschewski H, Olschewski A, Marsh LM, Kwapiszewska G. COMP as a possible negative regulator of TGF-beta signalling. Role in the right ventricular fibrosis. Meeting „4. Forschungswerkstatt - Pulmonary Hypertension", Feb 2015; Berlin, Germany.

Egemnazarov B, Crnkovic S, Olschewski H, Olschewski A, Marsh LM, Kwapiszewska G. The role of cartilage oligomeric matrix protein (COMP) in right ventricular fibrosis in the pressure overload model of right ventricular dysfunction in mice. ATS Conference, May 2015; Denver, US.

Egemnazarov B, Crnkovic S, Olschewski H, Olschewski A, Marsh LM, Kwapiszewska G. Cartilage oligomeric matrix protein (COMP) as an adaptive mechanisms to the pressure overload in the right ventricle. ÖGP Annual Meeting, Oct 2015; Graz, Austria.

Fischer C, Leithner K, Wohlkoenig C, Quehenberger F, Bertsch A, Olschewski A, Olschewski H, Hrzenjak A. Histone deacetylase inhibitor panobinostat reduces hypoxia-induced cisplatin resistance of non-small cell lung carcinoma via HIF-1α destabilisation. ÖGP Annual Meeting, Oct 2015; Graz, Austria.

Foris V, Kovacs G, Douschan P, Kqiku X, Hesse C, Avian A, Bachmaier G, Olschewski A, Olschewski H. Acute haemodynamic response of pulmonary hypertension patients during right heart catheterisation. ATS Conference, May 2015; Denver, US.

Foris V, Kovacs G, Douschan P, Kqiku X, Hesse C, Avian A, Bachmaier G, Olschewski A, Olschewski H. Clinical relevance of pharmacologic testing during right heart catheterisation. ÖGP Annual Meeting, Oct 2015; Graz, Austria.

Leithner K, Hrzenjak A, Trötzmüller M, Köfeler HC, Harris AL, Olschewski A, Olschewski H. Beyond Warburg effect: Adaptation to low glucose involves use of glutamine as alternative carbon source in lung cancer cells. ÖGP Annual Meeting, Oct 2015; Graz, Austria.

Marsh LM, Hoffmann J, Ghanim B, Klepetko W, Olschewski H, Olschewski A, Kwapiszewska G. Monocyte and dendritic cell populations in patients with diverse forms of pulmonary hypertension. Keystone Symposia, Feb 2015; Montreal, Canada.

Marsh LM, Hoffmann J, Ghanim B, Klepetko W, Olschewski H, Olschewski A, Kwapiszewska G. Diverse forms of pulmonary hypertension possess distinct inflammatory cell profiles. ATS Conference, May 2015; Denver, US.

Nagaraj C, Olschewski A, Marsh LM. Deletion of p22phox protects against house dust mite induced asthma in mice. COST Meeting, Jun 2015; Stockholm, Sweden.

Nagaraj C, Tang B, Jain P, Olschewski A. Specific activation of KCa channels contribute to omega 3 fatty acid – induced pulmonary vasodilation. Experimental Biology Conference, Mar 2015; Boston, US.

Nagaraj C, Tang B, Nagy B, Papp R, Jain P, Marsh L, Meredith A, Klepetko W, Ghanim B, Olschewski A. DHA facilitates rapid pulmonary arterial relaxation via KCa channel mediated hyperpolarisation in pulmonary hypertension. Wiener Klinische Wochenschrift 2015; 127(19-20):820-820. IF 0.836. ÖGP Annual Meeting, Oct 2015; Graz, Austria.

Olschewski A, Chandran N, Tang B, Jain P. Preferential activation of BKCa channels contribute to DHA-induced pulmonary vasodilation. ATS Conference, May 2015; Denver, US.

Papp R, Nagaraj C, Bálint Z, Nagy B, Stacher E, Ghanim B, Klepetko W, Kwapiszewska G, Olschewski A. The role of TMEM16A upregulation in the pathomechanism of idiopathic pulmonary hypertension. Ion Channel Symposium, May 2015; Copenhagen, Denmark.

Papp R, Nagaraj C, Bálint Z, Nagy B, Stacher E, Ghanim B, Klepetko W, Olschewski A. Increased expression of TMEM16A may lead to depolarisation of human pulmonary arterial smooth muscle cells in IPAH. Meeting „4. Forschungswerkstatt - Pulmonary Hypertension", Feb 2015; Berlin, Germany.

Pienn M, Bredies K, Stollberger R, Kovacs G, Olschewski A, Olschewski H, Bálint Z. Denoising algorithm for quantitative assessment of thoracic dual-energy computed tomography images Wiener Klinische Wochenschrift 2015; 127(19-20):815-815. IF 0.836. ÖGP Annual Meeting, Oct 2015; Graz, Austria.

Pienn M, Payer C, Kovacs G, Foris V, Urschler M, Olschewski A, Olschewski H, Bálint Z. Pulmonary arterial tortuosity as a non-invasive diagnostic tool for pulmonary arterial hypertension. Wiener Klinische Wochenschrift 2015; 127(19-20):822-822. IF 0.836. ÖGP Annual Meeting, Oct 2015; Graz, Austria.

Reiter U, Reiter G, Kovacs G, Adelsmayr G, Greiser A, Olschewski H, Fuchsjäger M. Native T1 times in the ventricular insertion-points detect pulmonary hypertension with high diagnostic accuracy. European Congress of Radiology, Mar 2015; Vienna, Austria.

Zabini D, Crnkovic S, Xu H, Tscherner M, Ghanim B, Klepetko W, Olschewski A, Kwapiszewska G, Marsh LM. High mobility group box-1 (HMGB1) regulates vascular remodelling processes via c-Jun. ATS Conference, May 2015; Denver, US.

Invited talks

Hoffmann J. Pulmonale Hypertonie: Ein Phänomen mit unterschiedlichen molekularen Grundlagen. PHeV Meeting, Oct 2015; Frankfurt, Germany.

Hoffmann J. Morphometrie und Genetik des pulmonalvaskulären Remodellings. PH-DACH Symposium, Nov 2015; Heidelberg, Germany.

Kwapiszewska G. Meprins in lung diseases. SFB 877, Jan 2015; Kiel, Germany.

Kwapiszewska G. Vascular remodelling in lung diseases. COST Meeting, Jun 2015; Stockholm, Sweden.

Marsh LM. High altitude and asthma. COST BM1201 Winter Training School, Nov 2015; Borstal, Germany.

Olschewski H. Pulmonale Zirkulation. Supported by Actelion Pharmaceuticals Austria GmbH. Medical University of Graz, Mar 2015; Graz, Austria.

Olschewski H. Rehabilitation with exercise training in patients with pulmonary hypertension. ATS Conference, May 2015; Denver, US.

Pienn M, Helmberger M, Payer C, Kovacs G, Foris V, Stollberger R, Olschewski A, Olschewski H, Urschler M, Bálint Z. Quantification of lung vessel tortuosity in pulmonary hypertension patients. VU University Medical Centre, Mar 2015; Amsterdam, The Netherlands.

Citable conference proceedings

Douschan P, Kovacs G, Foris V, Avian A, Olschewski A, Olschewski H. Frequency of cardiopulmonary comorbidities in patients with pulmonary hypertension. Am J Respir Crit Care Med 191: A3844. ATS Conference, May 2015; Denver, US.

Egemnazarov B, Crnkovic S, Olschewski H, Olschewski A, Marsh LM, Kwapiszewska G. The role of cartilage oligomeric matrix protein (COMP) in right ventricular fibrosis in the pressure overload model of right ventricular dysfunction in mice. Am J Respir Crit Care Med 191: A5539. ATS Conference, May 2015; Denver, US.

Fischer C, Leithner K, Wohlkoenig C, Quehenberger F, Bertsch A, Olschewski A, Olschewski H, Hrzenjak A. Histone deacetylase inhibitor panobinostat reduces hypoxia-induced cisplatin resistance of non-small cell lung carcinoma via HIF-1α destabilisation. Wiener Klinische Wochenschrift 127: 816-817. Annual ÖGP Annual Meeting, Oct 2015; Graz, Austria.

Foris V, Kovacs G, Douschan P, Kqiku X, Hesse C, Avian A, Bachmaier G, Olschewski A, Olschewski H. Acute haemodynamic response of pulmonary hypertension patients during right heart catheterisation. Am J Respir Crit Care Med 191: A4784. ATS Conference, May 2015; Denver, US.

Leithner K, Hrzenjak A, Trötzmüller M, Köfeler HC, Harris AL, Olschewski A, Olschewski H. Beyond Warburg effect: Adaptation to low glucose involves use of glutamine as alternative carbon source in lung cancer cells. Wiener Klinische Wochenschrift 127: 816-816. ÖGP Annual Meeting, Oct 2015; Graz, Austria.

Marsh LM, Hoffmann J, Ghanim B, Klepetko W, Olschewski H, Olschewski A, Kwapiszewska G. Diverse forms of pulmonary hypertension possess distinct inflammatory cell profiles. Am J Respir Crit Care Med 191: A1977. ATS Conference, May 2015; Denver, US.

Olschewski A, Chandran N, Tang B, Jain P. Preferential activation of BKca channels contribute to DHA-induced pulmonary vasodilation. Am J Respir Crit Care Med 191: A1928. ATS Conference, May 2015; Denver, US.

Payer C, Pienn M, Bálint Z, Olschewski A, Olschewski H, Urschler M. Automatic artery-vein separation from thoracic CT images using integer programming. Lecture Notes in Computer Science 9350. 18th International Conference on Medical Image Computing and Computer Assisted Intervention, Oct 2015; Munich, Germany.

Pienn M, Payer C, Olschewski A, Olschewski H, Urschler M, Bálint Z. Increased tortuosity of pulmonary arteries in patients with pulmonary hypertension in the arteries. Proceedings of the 19th Annual Conference in Medical Image Understanding and Analysis. MIUA Conference 2015, Jul 2015; Lincoln, UK.

Reiter U, Reiter G, Kovacs G, Adelsmayr G, Greiser A, Olschewski H, Fuchsjäger M. Native T1 times in the ventricular insertion-points detect pulmonary hypertension with high diagnostic accuracy. EPOS - Electronic Presentation Online System. European Congress of Radiology, Mar 2015; Vienna, Austria.

Reiter U, Reiter G, Kovacs G, Adelsmayr G, Greiser A, Olschewski H, Fuchsjäger M. Left ventricular myocardial remodelling in pulmonary hypertension: a non-contrast magnetic resonance T1 mapping study. Insights Imaging 6 (Suppl 1): 172-172. European Congress of Radiology, Mar 2015; Vienna, Austria.

Reiter G, Reiter U, Kovacs G, Janig C, Olschewski H, Fuchsjäger M. Magnetic resonance imaging-based diagnosis of pulmonary hypertension: 4D flow versus standard functional indices. Insights Imaging 6 (Suppl 1): 247-247. European Congress of Radiology, Mar 2015; Vienna, Austria.

Zabini D, Crnkovic S, Xu H, Tscherner M, Ghanim B, Klepetko W, Olschewski A, Kwapiszewska G, Marsh LM. High mobility group box-1 (HMGB1) regulates vascular remodelling processes via c-Jun. Am J Respir Crit Care Med 191: A1971. ATS Conference, May 2015; Denver, US.

3. Teaching and Training Activities of the Institute

3.1. Teaching Activities of the Members of the Institute

Andrea Olschewski is involved in teaching at different levels at the MUG. She gives student lectures in the Human Medicine Diploma Programme (Anaesthesiology, Intensive Care Medicine and Pain Therapy) and seminars as well as practical courses for PhD doctoral studies (MOLMED and MOLIN). She supervises either as a principal investigator or as a member of the dissertation committee of students (PhD or Dr.sci.med.): Neha Sharma, and co-supervises Bence Nagy, Vasile Foris, Philipp Douschan, Anna Gungl, Jovana Maric, and Elvira Stacher.

Grazyna Kwapiszewska is currently supervising Anna Gungl (PhD Programme Molecular Medicine) and co-supervising Elvira Stacher (Dr. sci. med) and Master student Lena Mischkulnig. She also gives seminars and practical courses in the PhD Programme Molecular Medicine at the MUG.

Leigh Marsh is a member of the thesis committee for Anna Gungl and Vasile Foris of the PhD Programme Molecular Medicine. He is teaching in the PhD Programmes Molecular Medicine and Molecular Inflammation at the MUG.

Zoltán Bálint is currently co-supervising the PhD student Michael Pienn. He is teaching in the PhD Programme Molecular Medicine at the MUG.

Gabor Kovacs is currently supervising the PhD student Vasile Foris and the Dr. scient med. student Philipp Douschan. In addition, in 2015 he had teaching activities within the frame of Modul 28 at the MUG.

Andelko Hrzenjak offers twice per year two seminars, “Basics in molecular biology” and “Protein expression systems”, for PhD students and once a year the seminar “Molecular biology in medicine" for medical students. He supervises Beatrix Wieser (Master thesis, TU/UNI Graz) and Thomas Heitzmann (Master thesis, MEDUNI Graz).

Horst Olschewski supervises the PhD students Vasile Foris and Bence Nagy as well as the Dr. scient. med students Xhylsime Kqiku, Philipp Douschan, Michael Palfner, Irina Fadejeva, and Elisabeth Smolle. He has reviewed the Habilitationsschrift of Dr. Schütz, University of Ulm Germany. He has been teaching in Modul 28, Modul 58, and Modul 16 at the MUG and given several lectures in the postgradual programme of the University Hospital of Internal Medicine and many lectures in other programmes. He has been holding a dissertation seminar every year.

3.2. Training in the LBI for Lung Vascular Research

Training of students and postdoctoral fellows is one of the most important functions of our group leaders and professors. We encourage our fellows to attend major international meetings, including the European Respiratory Society, American Thoracic Society, American Heart Association, Experimental Biology, and Gordon and Keystone Conferences. Presentations at these meetings help to broaden their research experience, improve their networking skills and give them international exposure.

Lab Meetings: Each research group holds weekly research meetings. Here the entire staff participates in the discussion and interpretation of the ongoing research, the planning and design of new studies, publication strategy and group organisation.

Weekly Seminar Series: Additional regular formal meetings ensure continued communications between the multidisciplinary investigators within the institute. To this end, we have a weekly seminar series from September to July. The seminar series rotates from one research group to another. The presentations have a broad format. The intention is to enable all of the investigators, fellows, and PhD or Master students to present work that is ongoing and not "the finished product." This format also encourages more interaction between the presenter and the attendees and gives the presenters the opportunity to get input about experimental design, data interpretation and presentation style.

Each group leader invites speakers from outside the institute to present formal seminars, usually once per year. The invited speakers generally spend at least one full day visiting the LBI-LVR groups (in this context, find the list of invited speakers 2015 below). The primary objective of these seminars is to enable all LBI-LVR investigators to interact with internationally recognised scientists and potentially develop research collaborations. The programme may also include short research presentations from junior colleagues and a buffet dinner.

Journal Club Seminars: The three research groups of our institute have a weekly journal club seminar. There, a topic related paper is presented and discussed. The seminars are implemented into the PhD programme Molecular Medicine of the MUG and so also several other PhD students join them.

Special Trainings:

Presentation Skills Training: Almost all scientists of the LBI-LVR participated in this interesting training by Dr. Isabel Landsiedler of the Graz Technical University in February 2015. Each participant had a presentation that was video taped and feed back was offered. Different presentation models were discussed. Special focus was placed on the preparation of questions of the audience as well as questions that arise after a given presentation.

Rhetorical Training: This training was tailor made for our research group leaders and key scientists. Again, it was Dr. Isabel Landsiedler of the Graz Technical University who offered this training in September 2015. It included vocal exercises, articulation drills and how to use visual language and rhetorical techniques. The participants had the possibility to present examples that where video-taped and analysed thereafter in order to receive valuable feedback.

Invited Speakers 2015

Name	Affiliation	Date	Title of the Talk
STEINBICKER Andrea, PD Dr.	Medical Faculty Münster, Germany	13 Jan 15	Iron homeostasis in pulmonary hypertension
HEINEMANN Akos, Prof.	Medical University of Graz, Austria	24 Feb 15	Role of prostanoids in eosinophil and neutrophil recruitment
EICKELBERG Oliver Prof.	Director, Institute of Lung Biology and Disease (iLBD), Comprehensive Pneumology Centre, Ludwig-Maximilians-University and Helmholtz Centre Munich, Germany	10 Mar 15	A personal journey of science and medicine
VOELKEL Norbert Prof.	Faculty Molecular Biology and Genetics at the Virginia Commonwealth University, Richmond, US	17 Mar 15	The landscape and spectrum of severe PAH and the implications for therapy
GÜNTHER Andreas Prof.	Universitätsklinikum Giessen und Marburg GmbH, Germany	5 May 15	Alveolar epithelial injury, repair and regeneration in lung fibrosis
HOLZER Peter Prof.	Medical University of Graz, Austria	23 Jun 15	Gut-brain communication driven by microbiota
ZAUKE Frank PD Dr.	Institute of Biochemistry II, University Köln, Germany	30 Jun 15	The role of thrombospondins in collagen homeostasis - implications for fibrotic diseases
ROSE-JOHN Stefan, Prof.	Institute of Biochemistry, Christian-Albrechts-University, Kiel, Germany	2 Nov 15	Interleukin-6 and ADAM17 in the regulation of inflammation and cancer
GRUNIG Gabriele Dr.	New York University School of Medicine, Tuxedo, US	11 Nov 15	Asthma, air pollution and pulmonary hypertension

Photo: Young scientists had the opportunity to join the lecture and discuss the topic with Prof. Voelkel in our LBI-LVR seminar room. Copyright: LBI-LVR

Photos: Young scientists enjoyed the scientific discussion with Prof. Holzer in the LBI-LVR. Copyright: LBI-LVR

Photos: PD Dr. Frank Zauke during his lecture in the LBI-LVR. Copyright: LBI-LVR


Photos: The event with Prof. Eickelberg was done as a co-operation with the Medical Studies and the PhD programmes of the MUG. Copyright: LBI-LVR

3.3. Graduate School

The LBI for Lung Vascular Research provides a doctoral training (PhD) within the multidisciplinary graduate training programme of the Medical University of Graz (MOLMED and MOLIN) and the Graz University of Technology. The highly competitive research schools offer an outstanding opportunity for education and research in a stimulating scientific environment and prepare students for their future careers with equal success in academia or industry. The PhD programme of the MUG is accredited by ACQUIN.

To learn about the PhD projects please got to:

MOLMED: http://www.medunigraz.at/phd-medizin/phd-programs/molecular-medicine/

MOLIN: http://www.medunigraz.at/DK-MOLIN/

In the LBI-LVR, doctoral and postdoctoral researchers are able to share their interests and become involved in new or related areas, particularly in confronting the major complex problems that necessitate exploration of ideas at the intersection of disciplines. The LBI-LVR encourages the fellows to attend major international meetings to broaden their research experience, improve their networking skills and give them international exposure.

3.4. Participation in the Scientific Community Service

Each group leader also actively participates in the scientific community service at the local, national and international levels. Within the Medical University of Graz, Andrea Olschewski, Grazyna Kwapiszewska, Zoltán Bálint, Gabor Kovacs and Horst Olschewski currently serve on promotion committees (PhD Programme), as members or chairs of research committees, the Personnel Development Advisory Board of the the Medical University of Graz (Horst Olschewski) for establishing new associate professors etc. At the national and international levels, the LBI-LVR group leaders serve on editorial boards, as reviewers for numerous journals (> 20 scientific journals), and as full-time or ad-hoc members of different Grant Review Panels (Andrea Olschewski: Swiss National Science Foundation; Anniversary Fund of the Oesterreichische Nationalbank, Austria; Canada Government, Canada; German Research Foundation (DFG) and von Behring-Röntgen-Foundation, Germany; Ministerium für Wissenschaft, Forschung und Kunst, Baden-Würtenberg, Germany). They also serve as advisors for pre-doctoral candidates and sit on dissertation committees. Kovacs, Douschan and Foris also have clinical duties at the Medical University of Graz / University Clinic Graz. Horst Olschewski is Chair of the Division of Pulmonology at the Medical University of Graz / University Clinic Graz and Andrea Olschewski is Chair of the Experimental Anaesthesiology at the Medical University of Graz.

4. Internal Activities of the Institute

Key Researcher Meetings

The LBI-LVR key researchers meet once in a month to discuss about budget and task distribution, research and various other open issues for the benefit of the institute. For internal organisation, a protocol is made in written form accessible to the key researchers.

Institute Meetings

The LBI-LVR and associate members meet four times per year in order to discuss organisational issues of the institute, task distribution, research and various other topics.

Photo: Team discussion in the LBI-LVR. Copyright: LBI-LVR/ Bergmann

LBI-LVR Annual Retreat Riegersburg

The annual retreat of the LBI-LVR took place at the Riegersburg on May 18th and 19th, 2015. In preparation for the up-coming SAB meeting, our scientists as well as the representatives of our partners came together in order to discuss the actual research results during five oral presentations and four poster sessions. The scientific programme was rounded off with a hiking tour to the Riegersburg castle.