

ANNUAL REPORT

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Partners

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



(Website: www.lbg.ac.at)

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

Medical University of Graz

(Website: www.medunigraz.at)

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



(Website: www.bayer.de)

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

Committees

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



Prof. Wolfgang Kübler – Charité - Universitätsmedizin Berlin, DE https://physiologie-ccm.charite.de/en/ Prof. Steve Abman – University of Colorado, US http://www.cudoctors.com/Find_A_Doctor/Profile/5902 Prof. Nick Morrell – University of Cambridge, UK http://www.med.cam.ac.uk/morrell/ Prof. Jose Lopez-Barneo – University of Sevilla, ES https://www.ibis-sevilla.es/investigacion/neurociencias/neurobiologia-celular-ybiofisica/lopez-barneo-jose.aspx Prof. Martin Kolb – McMaster University of Ontario, Canada https://fhs.mcmaster.ca/medicine/respirology/faculty_member_kolb.htm

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



Mag.a Caroline Schober-Trummler, Medical University of Graz

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



Dr.ⁱⁿ Heidrun Dorsch, Bayer AG http://pharma.bayer.com/



Dr. Peter Mayrhofer, Ludwig Boltzmann Gesellschaft http://www.lbg.ac.at/bereichsleitung

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 society (LBG). LBG founded institutes conduct research in the fields of Medicine & Life Sciences or Humanities. The LBI-LVR was established after a demanding two-stage evaluation by international peers who strongly recommended the founding of the institute.

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

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

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

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

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The scheme depicts the structure of our institute



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

In recent years, the area of lung vascular diseases has emerged as a leading field of medical research. In particular, the diagnosis and therapy of pulmonary hypertension (PH) has made tremendous progress over the past 25 years. This has started with the first approval of a drug for idiopathic pulmonary arterial hypertension in 1995 and resulted in 14 approvals of different drugs and applications up to the year 2019. All these approvals were based on international pivotal trials providing evidence for efficacy and safety for targeted drugs for PAH or chronic thromboembolic pulmonary hypertension. However, PH remains a notoriously under-diagnosed chronic and fatal disease. Therefore, early recognition of the disease is still crucial. As the diagnosis of PH is performed by invasive right heart catheterisation, the development of reliable non-invasive methods to assess increased pulmonary arterial pressure values may represent a unique selling proposition. An additional urgent challenge is the development of PH in chronic heart and lung diseases: large patient populations with severe left heart disease or chronic obstructive lung disease may develop PH during the course of their disease, but currently no effective

treatment options exist for these conditions. This represents an opportunity to develop novel concepts and therapeutic approaches.

Progressive loss of exercise capacity and worsening dyspnoea represent the most common symptoms of lung diseases, particularly if PH is involved. Clinical care for pulmonary vascular diseases is 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 far away from curing the disease or providing a substantially prolonged lifespan with a good quality of life. Future development must address these challenges in a multidisciplinary approach combining findings from basic research and clinical research.

1.2 Mission Statement/Aims of the Institute

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

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

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

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

1.3 Personal and Human Resources Development

1.3.1 Development of the LBI-LVR Staff

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

1.3.2 Graduations of the LBI-LVR Staff in 2019

In 2019, two colleagues had their graduations. We congratulate!

BIRNHUBER Anna

PhD Graduation, Defence in July, 2019 PHD Thesis: "IL-1 receptor blockade skews inflammation towards Th2 in a mouse model of systemic sclerosis"

BRCIC Luka

Habilitation in April, 2019 Habilitation in clinical pathology and molecular pathology





1.3.3 MUG takes over colleagues

In 2019 two of our colleagues were taken over by the Medical University of Graz. We congratulate!

CRNKOVIC Slaven

Univ.-Ass. Mag.rer.nat. PhD., Department of Physiology,

Medical University of Graz, Austria and Researcher at LBI LVR



JANDL Katharina

Univ.-Ass. Mag.rer.nat. PhD., Department of Pharmacology,

Medical University of Graz, Austria and Researcher at LBI LVR



1.3.4 Awards and prizes

Name	Awards 2019		
BIRNHUBER Anna	1st prize, poster awards at the Annual meeting of the Austrian Society		
	of Pneumology 2019, Vienna, Austria		
BONYADIRAD Ehsan	Wilhelm Auerswald Preis 2019, Vienna, Austria		
CRNKOVIC Slaven	Michel Neumann Gedächtnispreis 2019, Annual meeting of the Austrian Society of Pneumology 2019, Vienna, Austria		
EGEMNAZAROV Bakytbek	Michel Neumann Gedächtnispreis 2019, Annual meeting of the Austrian Society of Pneumology 2019, Vienna, Austria		
MUTGAN Ayse Ceren	3rd prize, poster awards at the Annual meeting of the Austrian Society of Pneumology 2019, Vienna, Austria		
FORIS Vasile	1st Prize, Research award at the Annual meeting of the Austrian Society of Pneumology 2019, Vienna, Austria		

Name	Travel Awards/Fellowships 2019		
CRNKOVIC Slaven	European Respiratory Society Long Term Scholarship, Perelman School of Medicine, University of Pennsylvania, Philadelphia, USA Ed Morrisey Lab, 2018 - (until march 2019)		
DOUSCHAN Philipp	ERS Abstract Travel Grant, Annual meeting of the Austrian Society of Pneumology, Vienna, Austria 2019		

1.3.5 Conferences and Meetings of the LBI-LVR Staff

Presentations at national and international conferences: Oral Communications

Birnhuber A. et.al. Targeting innate immunity exacerbates inflammation and pulmonary fibrosis in a systemic sclerosis-associated lung disease model; Austrian Society of Pneumology Annual Meeting 2019, October 10-12, 2019; Vienna, Austria (Talk)

Birnhuber A. et al. Anti-inflammatorische/anti-fibrotische Medikamente bei Systemischer Sklerose im Tiermodell. PH-DACH Herbstsymposium 2019; November 14-16; Heidelberg, Germany. (Talk)

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Birnhuber A. et.al. Targeting innate immunity exacerbates inflammation and pulmonary fibrosis in a systemic sclerosis-associated lung disease model; Austrian Society of Pneumology Annual Meeting 2019, October 10-12, 2019; Vienna, Austria (Oral Presentation for Poster Award)

Foris V. et.al. D-Dimer und NT-proBNP: klinische Relevanz in der Lungengefäßerkrankungen. Arbeitskreistreffen der ÖGP. April 12, 2019; Graz, Austria. (Talk)

Foris V et al. Zarte Frau, große Expansion. Jahrestagung der Österreichischen Gesellschaft für Pneumologie (ÖGP), Vienna, Austria, 10-12 October 2019 (Oral Presentation)

Jacob, J; Pienn, M; Payer, C; Urschler, M; Kokosi, M; Devaraj, A; Wells, AU; Olschewski, H. Normalized Vessel Volume from Quantitative Computed Tomography Predicts Survival in Idiopathic Pulmonary Fibrosis. International Conference of the American-Thoracic-Society 2019; Dallas, TX. (Oral Presentation)

Kovacs G. et.al. Normal PAP in healthy subjects – and beyond. PVRI Kongress. Feb 1 – Feb 3, 2019; Barcelona, Spain. (Talk)

Kovacs G. et.al. Spiroergometrie mit Fokus pulmonale Hypertonie. Internationaler Spiroergometrie Kurs. Feb 27 – Feb 28, 2019; Bern, Switzerland. (Talk)

Kovacs G. et.al. Diagnose einer PH. Arbeitskreissitzung des AK Pulmonale Zirkulation der ÖGP. April 4, 2019; Graz, Austria. (Talk)

Kovacs G. et.al. Pulmonale Druckwerte und Herzzeitvolumen, invasiv und nicht-invasiv. DGK Kongress. April 25, 2019; Mannheim, Germany. (Talk)

Marsh LM. Kommunikation zwischen Forschenden und Tierpflegepersonal. 3R Tage 2019, Graz, Austria (Oral Presentation)

Mutgan C et.al. Identifying the role of matrikines in pulmonary hypertension. MolMed PhD Program Project Presentation 2019; Graz, Austria. (Oral Presentation)

Mutgan C et al. Fragment of Collagen IV is a mediator of endothelial dysfunction in pulmonary hypertension. Annual meeting of the Austrian Society of Pneumology 2019, Vienna, Austria (Oral Presentation for Poster Award)

Nagy BM et.al. Metabolomics in pulmonary hypertension. Quadrilateral Physiology Symposium 2019; Graz, Austria. (Oral Presentation)

Nagy BM et.al. Metabolomics in pulmonary hypertension. Otto Loewi Research Center Seminar 2019; Graz, Austria. (Oral Presentation)

Presentations at national and international conferences: Posters

Barth, DA; Riedl, JM; Foris, V; Posch, F; Mollnar, S; Stotz, M; Pichler, M; Stöger, H; Absenger, G; Olschewski, H; Gerger, A. External validation and longitudinal extension of the LIPI for immunotherapy outcomes in advanced non-small cell lung cancer. Jahrestagung der Deutschen, Österreichischen und

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Schweizerischen Gesellschaften für Hämatologie und Medizinische Onkologie; 11. - 14. October 2019; Berlin, Germany

Bonheur S, Štern D, Payer C, Pienn M, Olschewski H, Urschler M. Matwo-CapsNet: A Multi-label Semantic Segmentation Capsules Network. MICCAI 2019: 22nd International Conference; October 13 -17, 2019, Shenzhen, China

Bordag N, Biasin V, Nagy BM, Sharma N, Jandl K, Kwapiszewska G, Marsh L. Modelling the inflammatory cell kinetics following bleomycin-induced lung injury. ÖGAI 2019: 47th Annual Meeting; November 21 - 23, Graz, Austria

Bruni C, Occhipinti M, Camiciottoli G, Bartolucci M, Pienn M, Lepri G, Fabbrizzi A, Tottoli A, Ciardi G, Giuggioli D, Cuomo G, Masini F, Olschewski A, Lavorini F, Colagrande S, Matucci-Cerinic M. Relationship between Parenchymal and Vascular Features in Systemic Sclerosis-Interstitial Lung Disease: Results from Quantitative Analysis of Chest Computed Tomography. 2019 ACR/ARP Annual Meeting; November 8 - 13 2019 in Atlanta, Georgia, USA

Crnkovic S, Basil M, Morely M, Jandl K, Zepp J, Marsh L, Kwapiszewska G, Morrisey E. Single Cell Resolution Reveals Cellular Diversity and Major Heterotypic Interactions in Pulmonary Vasculature. University of Pennsylvania Biomedical Postdoctoral Research Symposium; November 05, 2019, Philadelphia, PA, USA

Crnkovic S, Jandl K, Zabini D, Marsh LM, Sinn K, Klepetko W, Olschewski A, Kwapiszewska G. Adult Pulmonary Vascular Remodeling is Independent of Ephrin-b2/EphB4 Guidance System. Austrian Society of Pulmonology; October 10 - 12, 2019, Vienna, Austria

Crnkovic S, Egemnazarov B, Marsh LM, Sinn K, Klepetko W, Holzer P, Herzog H, Olschewski A, Kwapiszewska G. Increased Expression of NPY1R Mediates Increased Vascular Reactivity to NPY. Quadrilateral Physiology Symposium 2019; June 26, 2019 Graz, Austria

Foris, V; Kovacs, G; Avian, A; Douschan, P; Olschewski, H. Changes in blood derived biomarkers reflect PAH progression and response to targeted therapy. Jahrestagung der Österreichischen Gesellschaft für Pneumologie; October 10-12, 2019; Vienna, Austria

Nagy B; Papp R; Nagaraj C; Zabini D; Lengyel M; Maurer DS; Sharma N; Egemnazarov B; Kovacs G; Kwapiszewska G; Marsh LM; Hrzenjak A; Höfler G; Didiasova M; Wygrecka M; Sievers LK; Szucs P; Enyedi P; Ghanim B; Klepetko W; Olschewski H; Olschewski A, Targeting TMEM16A to reverse vasoconstriction and remodeling in idiopathic PAH. Keystone Symposium; March 15 - 19, 2019; Firenze, Italy

Nagy B; Kovacs G; Tornyos A; Svehlikova E; Foris V; Nagaraj C; Kwapiszewska G; Pieber RT; Olschewski A; Olschewski H, Is idiopathic pulmonary arterial hypertension caused by insulin resistance? Jahrestagung der Österreichischen Gesellschaft für Pneumologie; October 10 - 12, 2019; Vienna, Austria

Rosenstock, P; Avian, A; Douschan, P; Foris, V; Pienn, M; Sassmann, T; Olschewski, H; Kovacs, G. Realworld clinical management of CTEPH patients - a single center experience. Jahrestagung der Österreichischen Gesellschaft für Pneumologie; October 10 - 12, 2019; Vienna, Austria

1.3.6 Patents of the LBI-LVR

Patents	Inventors	
Biomarker for the diagnosis of pulmonary	H. Olschewski (LBI-LVR), A. Olschewski (LBI-LVR), CH.	
hypertension (PH)	Magnes (Joanneum Research), N. Bordag, S. Narath	
Patent No. 16159415.5	(CBmed GmbH), E. Gander (Joanneum Research)	
	and B. Nagy (LBI-LVR)	
Method for non-invasive diagnosis of pulmonary	M. Pienn (LBI-LVR), H. Olschewski (LBI-LVR), G.	
hypertension. Method for processing images of	Kovacs (LBI-LVR) and Z. Bálint (LBI-LVR)	
the pulmonary circulation and apparatus for		
carrying out this method.		
Patent No. A 50719/2016.		
Method and apparatus for processing	M. Pienn (LBI-LVR), H. Olschewski (LBI-LVR), G.	
impedance cardiograms for the assessment of	Kovacs G., Z. Bálint.(LBI-LVR)	
the presence of pulmonary hypertension of a		
Patient and impedance cardiograph with such a		
device		
Patent No. 518396/2017		
Modulation of the calcium-activated chloride	A. Olschewski (LBI-LVR), B. Nagy (LBI-LVR), Chandran	
channel including TMEM16A represent a novel	Nagaraj (LBI-LVR), Rita Papp (LBI-LVR)	
therapy for pulmonary hypertension (PH)		
Sold to Bayer AG		

1.4 Highlights 2019

1.4.1 LBI-LVR moved on new MED CAMPUS Graz

At the beginning of the year 2019, our institute moved to the new MED CAMPUS Graz. Here we can use spacious laboratory areas and beautiful office space to advance our research.



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1.4.2 Affiliated Partner of ERN LUNG



Respiratory Diseases (ERN-LUNG)

Center for pulmonary hypertension as part of the European reference network for rare lung diseases

The Ludwig Boltzmann Institute for Lung Vascular Research and the Clinical Department for Lung Diseases of the University Hospital for Internal Medicine at the LKH University Hospital / Medical University Graz, under the direction of Prof. Horst Olschewski, in cooperation with other clinical departments was officially announced in 2019 as a new affiliate partner in the European reference network for rare lung diseases (ERN-LUNG).

Participation in the reference network takes place as a center for pulmonary hypertension.

European Reference Networks (ERN) are cross-border virtual networks of centers of expertise and healthcare providers. The goal of these networks is to provide improved access to high quality diagnostics, care and treatment by pooling knowledge and experience, medical research and education, as well as other resources in the field of rare diseases or rare complex conditions.

More information can be found at: <u>https://ern-lung.eu/</u>

1.4.3 Awards

Wilhelm-Auerswald-Prize 2019

On May 21, 2019, the "Wilhelm Auerswald Prize" for the best doctoral thesis at an Austrian Medical University was awarded for the 28th time in the Billrothhaus in Vienna. Ehsan Bonyadirad, PhD, received the sixth prize for his work "Expression, Regulation, and Function of ST2 / IL1RL1 in Growth Plate Chondrocytes.



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Awards at the ÖGP Annual Conference 2019 for the LBI-LVR

The staff of the Ludwig Boltzmann Institute and the Pulmonology Clinical Unit for Pulmonary Vascular Research was extremely successful at the 43rd Annual Meeting of the Austrian Society for Pulmonology (ÖGP), which took place from 10 to 12 October 2019 at the Congress Center / Reed Messe in Vienna. Five high-ranking prizes went to Graz.

In addition to the awards for the first and third place of the competitive scientific poster award for basic research, a young clinical scientist was awarded a travel grant to the ERS (European Respiratory Society), another received this year's ÖGP science funding and also the most highly endowed ÖGP research award Michael Neumann Memorial Award, went to our young research team from Graz for their joint scientific publication in the highest international respiratory journal, the American Journal of Respiratory and Critical Care Medicine.

The winners in detail:

- EGEMNAZAROV Bakytbek and CRNKOVIC Slaven: Michael Neumann Memorial Award
- FORIS Vasile: Science Funding 2019
- BIRNHUBER Anna: 1st poster prize (basic research)
- MUTGAN Ayse Ceren: 3rd poster prize (basic research)
- DOUSCHAN Philipp: ERS Travel Grant 2019



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1.4.4 Fellowships

Slaven Crnkovic awarded the European Respiratory Society Long-Term Fellowship

Slaven Crnkovic, a postdoctoral researcher at LBI for Lung Vascular Research, has been awarded the European Respiratory Society Long-Term Fellowship to support his research stay in the laboratory of Prof. Edward Morrisey at Perelman School of Medicine, University of Pennsylvania. Prof. Morrisey is one of the world's leading pulmonary biologists and at the forefront of using novel research techniques deciphering the mechanisms behind normal and pathological lung development.

1.4.5 Grants

FWF Grant for Slaven Crnkovic

Slaven Crnkovic, PhD, has received the ERA CVD JTC Grant for his project "IMPHLeXIONS". This is a FWF grant for Transnational Cardiovascular Research Projects driven by Early Career Scientists. Start of the project is announced for May 2020.



ÖGP Science funding for Vasile Foris

The Austrian Society of Pneumology promotes the implementation of scientific studies and projects in Austria. At the Annual Meeting in Vienna, Vasile Foris, PhD, has received the grant called "ÖGP Wissenschaftsförderung" for his project "Changes in blood derived biomarkers reflect PAH progression and response to targeted therapy".

Medical University of Graz Start funding for Katharina Jandl

The Medical University of Graz promotes the implementation of scientific studies and projects of young scientists. Katharina Jandl, PhD, has received this Grant for her project called "The role of the PGE2-EP4 axis in pulmonary arterial hypertension".





1.4.6 Events





The Quadrilateral Physiology Symposium 2019 took place on 21st June, 2019 in Graz. It was organized in cooperation of the Austrian, Slovenian, Croatian, and Slovakian Physiological Society and the LBI-LVR under the theme "Vascular Physiology, Physiological Techniques and Medical Education". The invited speakers were from the Association of Physiologists and Pharmocologists of India (APPI), the Czech Physiological Society, the French Physiological Society and the Physiological Society of south Africa.







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SAB Retreat Hotel Retter Pöllauberg, Styria 2019

Our annual retreat took place on September 12th - 13th, 2019 in the Hotel Retter – Pöllauberg in Styria. Our young colleagues presented their ongoing projects and discussed their findings. After each presentation, there was a lively discussion among the participants. In the evening, these discussions were continued on a joint hike to the pilgrimage church on Pöllauberg.







© LBI LVR

CPX-Congress - European Practicum on Cardiopulmonary Exercise Testing in Graz

The international CPX Congress took place from 18 to 20 September 2019 at the Medical University of Graz under the patronage of the ÖGP and the Ludwig Boltzmann Institute for Lung Vascular Research. At this congress the theoretical background and practice of exercise-testing was presented by international experts. Special point of the conference was the use of exercise testing in patients with lung vascular diseases.





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SAB Meeting 2019 in Graz

On 11 November, the seventh Scientific Advisory Board Meeting took place in the new complex of the Medical University of Graz (ZMF II). The SAB members **Prof. Wolfgang Kuebler** (Charité Berlin), **Prof. Jose Lopez-Barneo** (University of Sevilla), **Prof. Steve Abman** (University of Colorado) and **Prof. Nicholas Morrell** (University of Cambridge) visited the Ludwig Boltzmann Institute for the annual review of the scientific progress. We were glad to present our scientific process at this meeting and we want to thank our SAB members for the stimulating discussions. Our Board Members **Dr. Heidrun Dorsch** (Bayer AG), **Dr. Peter Mayrhofer** (Ludwig Boltzmann Gesellschaft) and **Mag. Caroline Schober-Trummler** (Medical University of Graz) also participated in our annual meeting.





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1.5 Public Relations

Co-creation workshop for communication and use of medical research results CONNECT

In November, the first co-creation workshop of the CONNECT project took place in cooperation between the MedUni Graz (Selma Mautner), the Ludwig Boltzmann Gesellschaft (Ludwig Boltzmann Institute for Lung Vascular Research - Grazyna Kwapiszewska) and the Copenhagen Business School (Marion Pötz). The CONNECT project is developing a new process that enables different users of medical research results to participate in the development of new research projects in an innovative, open manner and at eye level. The Co-Creation Workshop was a first step towards achieving this goal: Researchers, doctors from various disciplines, patients, relatives, therapists and nurses have jointly developed opportunities to communicate the latest results from fibrosis research in such a way that they are easy accessible and enable users to contribute their own experiences. The type of communication developed in the workshop will subsequently be used in a crowdsourcing process in order to give a voice to many patients suffering from fibrosis and also to give a voice to those continuously supporting them such as their family, doctors, therapists or nurses. This innovative communication platform will allow people to participate in a process for the joint development of new research projects in the field of fibrosis.







Patient meeting on October 7th, 2019 - A Joint information day for patients with pulmonary fibrosis and / or pulmonary hypertension and relatives

This year the PH patient meeting took place with 60 participants at the Austria Trend Hotel in Graz. **Eva Otter** from PH Austria Initiative "Lungenhochdruck" welcomed the participants and gave an overview of the activity of their Initiative. Gabor Kovacs took over the Presentation of Horst Olschewski's talk, titled "6th PH World Congress - new recommendations - what is important for patients?" Here, the focus was placed on the practical changes in the care of Pulmonary hypertension patients after the last World Congress. Philipp Douschan informed about the Topic "Lung high pressure and concomitant diseases". After that, Andreas Zirlik moderated the 2nd part of the event. Robert Maier from the Cardiology department of LKH Univ. Klinikum Graz spoke about "heart ultrasound examinations at patients with pulmonary hypertension". Klemens Ablasser presented the part of Friedrich Fruhwald "LH at Left heart disease - current recommendations".





C LBI LVR

Comparative Healthcare Austria-Slovenia-US

On May 15th 2019, we welcomed a group of 26 American students from the University of Pittsburgh to the Ludwig Boltzmann Institute for Lung Vascular Research.

These students were inscribed in a five-week "Comparative Healthcare" program at the University of Pittsburgh, with the aim to explore healthcare through a comparative lens, using Austria and Slovenia as specific examples to contrast with the United States.

This program is a cooperation between the University of Graz and Pittsburgh and allows the students to meet and engage with local doctors, scientists and administrators while visiting various health care facilities not only in Graz but also Maribor, Salzburg and Vienna. In that way the students learn how culture and health relate to one another, how trends emerge in health care and how to look at the evolution of the health care system over time.

Diana ZABINI guided the interested students through the institute's rooms and laboratories and gave them an insight into the field of scientific and clinical research. In the concluding discussion, questions were answered and experiences exchanged.



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Newsletter

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



Press Appearances

The LBI for Lung Vascular Research has received several invitations to present their research work and aims to the broad public. A short overview of the **press appearances in 2019** is given here:

- "Fortschritt bei seltenen Erkrankungen" Der Grazer am 24.02.2019
- "Der Faschingsdienstag bleibt mir ewig in Erinnerung" Kronenzeitung am 09.03.2019
- "Krankheitsgeschehen zu erkennen hilft heilen" Kronenzeitung am 09.03.2019
- "Praxisrelevante Ergebnisse des 6. Weltsymposiums für pulmonale Hypertonie" universimed 16.07.2019
- "Wissenschaft und Pneumologie: neue Studien aus Österreich" universimed 05.09.2019
- "Ausgezeichnet: LBI LVR" medunigraz.at 14.11.2019

2 Research Program 2019

2.1 Pathomechanisms of Pulmonary Vascular Remodelling



In 2019 several crucial studies from our group contributed to the understanding of mechanisms underlying vascular remodeling in the diverse forms of pulmonary hypertension. Our studies could potentially help shape the directions where new therapeutic options could be developed.

Pulmonary hypertension and lung fibrosis in systemic sclerosis

Systemic sclerosis/scleroderma (SSc) is a systemic disease that involves several organs, including the skin, kidneys but also the lung. Involvement of the lung has a severe impact on the life and survival of SSc patients. Due to its negative influence on patient outcome, novel treatments remain an unmet medical need. In recent years, a mouse model was created that mimics several features of SSc. Mice overexpressing a transcription factor called Fos-related antigen-2 (Fra-2) develop a phenotype like SSc

patients, including systemic inflammation with pulmonary hypertension and fibrosis (Eferl et al. PNAS 2008). In a current review we thoroughly described the pulmonary phenotype of this model and the role of the Fra-2 transcription factor in the development of lung disease. We have highlighted and discussed the molecular mechanisms of Fra-2 which influence the development of pulmonary fibrosis, inflammation, parenchymal remodeling, and pulmonary arterial hypertension.



Figure 1: Pulmonary remodeling in Fra-2 overexpressing mice. A) Schematic representation of the pulmonary alterations in Fra-2 transgenic (Tg) mice. B) In mice, Fra-2 overexpression induces pronounced inflammatory cell recruitment and structural alteration; hematoxylin and eosin (HE) staining (upper panel). Masson's trichrome staining with shows increased collagen deposition (in blue) in remodeled vessels of Tg mice. Dual immunohistochemistry for the endothelial cell marker von Willebrandt-factor (VWF) and alpha-smooth muscle actin (α -SMA) highlight the increased muscularization associated with vessel remodeling (lower left panel). Vascular remodeling is accompanied by perivascular CD45-positive inflammatory infiltrates (lower middle panel). At later stages, remodeling in the parenchyma occurs, with elevated collagen deposition and occurrence of α -SMA-positive myofibroblasts in the parenchyma of Fra-2 Tg mice (lower right panel). (Figure modified from Birnhuber et al., Cell Signal. 2019 Dec;64:109408.)

This model represents a valuable tool to investigate pulmonary alterations associated with SSc and is frequently used at the LBI-LVR to assess therapeutic effects of repurposed or novel drugs to treat PH and/or lung fibrosis. A recent study from our laboratory investigated the role of interleukin-1 (IL-1) cytokines in the development of SSc-associated lung disease and whether IL-1 contributes to vascular and parenchymal remodeling. IL-1 levels in the lungs of SSc patients as well as in the Fra-2 Tg mouse model were measured. Further, a detailed characterization of hemodynamics, lung function and inflammatory profiles in Fra-2 Tg mice treated with an IL-1 signaling blocker was performed. In addition to these *in vivo* measurements, IL-1 effects on human parenchymal fibroblasts and pulmonary arterial smooth muscle cells were analyzed *in vitro*. Surprisingly, we found that pharmacological blockade of IL-1 signaling had detrimental effects of lung function. Due to skewing of inflammation towards an increased Th2 inflammatory response, it increased levels of pro-fibrotic, alternatively activated macrophages which further worsened the pathological processes in the lung.

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Figure 2: Blocking of IL-1 signaling worsens lung function and increases extracellular matrix production and the levels of profibrotic, alternatively activates macrophages. A) Lung function measurements of Fra-2 TG and WT mice with anakinra treatment or vehicle control (saline; IC: inspiratory capacity; Crs: compliance of the respiratory system); #: p<0.05, significance of genotype effect determined by two-way ANOVA; ¶: p<0.05, significance of the difference between Fra-2 TG with and without anakinra treatment determined by two-way ANOVA with Bonferroni's post-test). B) Correlation plots of Cst (quasi-static Compliance) with bronchoalveolar lavage (BAL) total cell count. C) Immunofluorescence staining of the alternatively activated macrophage marker RELM α (red), the macrophage marker CD68 (green), collagen (COL1, white) and DAPI (nuclei; blue). Arrows: CD68+/RELM α + double-positive cells, indicating pro-fibrotic alternatively activated macrophages. Scale bar: 25 µm. (adapted from Birnhuber et al. Eur Respir J. 2019 Sep 29;54(3).)

These results highlight the importance of a good and detailed understanding of disease pathomechanisms underlying pulmonary hypertension and/or fibrosis associated with SSc, to develop successful treatment strategies while avoiding unnecessary and severe adverse effects. This research work was recently awarded with the 1st poster prize at the Austrian Pneumology Society meeting in Vienna 2019 and the prestigious prize of the René Baumgart-Stiftung for excellent publications in the field of pulmonary hypertension.

Right ventricular fibrosis and dysfunction: Actual concepts and common misconceptions

Pulmonary arterial hypertension (PAH) is a disease that originates in pulmonary arteries, but ultimately affects right side of the heart - the right ventricle (RV). In fact, survival of PAH patients depends on how well and how long can the RV adapt to progressive pulmonary vascular disease. In addition to RV enlargement, fibrosis - loss of cardiomyocytes and replacement with scar tissue - is a common histological finding. This scarring process is thought to negatively influence the RV function. Deposition of various extracellular matrix components and expansion of fibroblasts in regions where under normal conditions cardiomyocytes are present, is thought to impair RV contraction-relaxation and proper conduction of electrical signals in the heart. In our recent study, we could show that the RV fibrosis from PAH patients and different animal models shares same pattern of marker expression and similar histological findings (Figures 1, 2). As a next step, we asked what would happen with RV function if we prevented or ameliorated the RV fibrosis. For this we relied on animal studies since human RV samples are rare and available mostly as archival pathological samples, which makes it impossible to test various therapeutic approaches. Most of the currently published preclinical studies investigating therapeutic interventions to improve RV function has reported concomitant reduction in RV fibrosis levels. While this might be regarded as a strong indication and evidence that improvement of RV function is directly dependent on amelioration of fibrosis, a closer look at the available literature raises doubts (Matrix Biol. 2018 Aug;68-69:507-521). We discovered that in all of the reports it is not possible to exclude direct effect of the therapeutic intervention on cardiomyocytes, an effect that would be fully sufficient to explain improved RV functional parameters. In fact, in our recent study show exactly such decoupling of RV fibrosis and RV function. In collaboration with researchers from Berlin, Germany and Johns Hopkins University, USA, we could show that reduction in RV fibrosis under different therapeutic interventions was not accompanied by improvements of RV function (Am J Respir Crit Care Med. 2019 Jun 15). Practical consequence of this finding is for the development of novel therapies: in light of our results new therapeutic options should focus on improving and preserving the cardiomyocyte function, rather than ameliorating fibrosis. More detailed implication of the fibrosis in the RV function have been discussed in the editorial written to this paper (Am J Respir Crit Care Med 199:12). For this study our colleagues have been rewarded with Michael Neumann Memorial Award at the Austrian Pulmonology Society meeting in Vienna 2019.



Figure 1: Representative immunohistochemical staining of control and diseased mouse and rat right ventricles against various molecular markers of fibrosis: vimentin, platelet-derived growth factor receptor alpha (PDGFR α), alpha smooth muscle actin (α SMA). Fibrotic regions were detected by sirius red staining and marked by an arrow. Noticeable is the general lack of myofibroblasts (arrowheads). Adapted from Crnkovic et al. AJRCCM 2019



Figure 2: Representative immunohistochemical staining of human RV from PAH patient against fibrotic markers (vimentin, platelet-derived growth factor receptor alpha (PDGFR α), alpha smooth muscle actin (α SMA)). Fibrotic regions were detected by sirius red staining and marked by an arrow. Noticeable is the general lack of myofibroblasts (arrowheads). Adapted from Crnkovic et al. AJRCCM 2019

Ion Channels in Pulmonary Hypertension: A Therapeutic Interest?

The pulmonary circulation is a low-pressure, low-resistance system. The low vascular tone of the pulmonary vasculature is largely maintained by the resting membrane potential of the pulmonary artery smooth muscle cells (PASMCs), which is mainly regulated by ion channels and its conductance .Thus, changes in both channel activity and expression have a direct impact on the resting membrane potential of PASMCs, thereby affecting the pulmonary vascular tone. There are hints from the literature that PASMCs from idiopathic PAH patients may have a more depolarised membrane potential (they are chronically depolarised) contributing to vasoconstriction and remodeling. In the recent review, we postulated that lon channels could serve as therapeutic option for pulmonary hypertension (Lambert et al Int J Mol Sci. 2018). Chronic membrane depolarization and Ca2+ overload are the result of the altered expression and function of different ion channels and transporters, as well as Ca2+ handling proteins. It is long been known that Ca2+-activated Cl– currents are present in SMCs, but little attention has been paid to anion channels in IPAH.

Our study published in the European Respiratory Journal (ERJ), Papp et al. 2019 address a systematic investigation of the compartment-specific regulation of Cl– channels and transporters in the pulmonary artery and in primary cultured PASMCs from IPAH patients showed strongly increased TMEM16A expression. Our study, however, is the first to demonstrate that these changes are very consistent in human PASMCs obtained from a large number of IPAH patients. Our study is also the first experimental investigation of the effects of TMEM16A inhibition and overexpression in human PASMC. In IPAH, TMEM16A was strongly upregulated and patch-clamp recordings confirmed an increased Cl– current in PASMCs. These cells were depolarized and could be repolarized by TMEM16A inhibitors or knockdown experiments. Inhibition/knock-down of TMEM16A reduced the proliferation of IPAH-PASMCs. Conversely, overexpression of TMEM16A inhibition reduces the increased pulmonary vascular tone both ex-vivo and in-vivo settings. Chronic application of benzbromarone in two independent animal models significantly decreased right ventricular pressure and reversed remodeling of established pulmonary hypertension.

The editorial to our article by AL Theilmann et al. ERJ 2019 "Repurposing benzbromarone for pulmonary arterial hypertension: can channelling the past deliver the therapy of the future?" - Postulating that this study, suggesting benzbromarone becomes the latest addition to a long list of existing drugs, including dichloroacetate , tacrolimus , hydroxychloroquine. Which are also being considered for repurposing as a PAH therapy. Drug repurposing offers a great advantage for rare and deadly diseases like PAH by allowing for the fast tracking of regulatory approval, while minimizing the costs associated with new

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drug development. Targeting altered anion flux could open up new therapeutic options for a currently undefined set of patients. The findings that TMEM16A modulation could serve for diagnostic or therapeutic use in PH has been patented- WO2018202471A1-)



Figure 1: TMEM16A influences membrane potential in human pulmonary artery smooth muscle cells (PASMCs). a) Effect of benzbromarone (BBR) on ICICa density in the PASMCs of IPAH patients. b) Membrane potential (Em) values obtained from PASMCs of healthy donors and IPAH patients in the absence (vehicle) or presence of the TMEM16A blockers T16Ainh-A01 (T16) or BBR. c) Em of PASMCs 72 h after transfection with either non-silencing control RNA (NS) or TMEM16A siRNA (SI). From Papp et al. ERJ 2019



Figure 2: The summarised functional consequences of TMEM16A overexpression in IPAH. From Papp et al. ERJ2019

Effect of TMEM16A upregulation on the resting membrane potential in PASMC and its pathophysiological consequences. The membrane potential (Em) of the PASMCs is the key to determining the intracellular Ca2+ concentration [Ca2+]i and the function of the pulmonary artery. The

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Em of a healthy PASMC is around –50 mV. Only a few TMEM16A channels are present and they are not active. Owing to the negative Em, voltage-gated Ca2+ channels (VGCC) are closed, and [Ca2+]i is low. In contrast, the overexpression and increased activation of TMEM16A channels represent a depolarizing current, raising Em to around –30 mV. The subsequent VGCC opening increases [Ca2+]i, leading to PA contraction and PASMC proliferation. From Papp et al. ERJ 2019.

Scientific Cooperations

ALLANORE Yannick M.D., Cochin Hospital, Paris, France BELLUSCI Saverio, PhD., Justus Liebig University, Giessen, Germany EFERL Robert Dr., Medical University of Vienna, Austria HASSOUN Paul M., M.D., Johns Hopkins University, Baltimore, Maryland 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 MORRISEY Ed Prof., University of Pennsylvania, Philadelphia, USA PEREZ Vinicio de Jesus, M.D., Stanford University, Stanford, California 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 Translation Platform of the LBI-LVR



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Two thousand and nineteen was a highly productive year for the Translational Platform, we contributed to eight collaborative peer reviewed manuscripts, both from within and without the LBI-LVR. We additionally, published one editorial and a JOVE article describing how to perform non-invasive echocardiography of the right ventricle in small animals. The latter especially underlines the importance and relevance of using clinically relevant readouts in pre-clinical studies. The team also attended the annual meeting of the Austrian society of immunology (ÖGAI: <u>http://www.oegai.org/oegai/</u>), which was held in at the Medical University in Graz.

We also welcomed our new technician, Kerstin Schweighofer to the Translational Platform. Since joining the Translational Platform in 2018, our part-time post-doctoral scientist, Natalie Bordag has dedicated herself to strengthened our data analysis methods. By applying her vast experience in high-end data analysis and interpretation, we have now gained new insights in ongoing and historical projects. Her research focus is to combine clinical with high-dimensional read-outs to generate foremost understandable, actionable knowledge, a wish of clinicians and biologists alike. Most real-world results are complex, often unbalanced and peppered with various data quality issues, despite best possible care of involved researches. To efficiently counteract these challenges, she has developed thorough quality control protocols and applies robust statistical methods. In order to decrease analysis time, we now apply semi-automated workflows to exploit the strengths of data-prepossessing, classical statistics and state-of-the art machine learning methods. We have applied these approaches to gain a deeper understanding of inflammatory cell changes during experimental pulmonary fibrosis. These studies build on our existing expertise in computational analysis as described in our recent 2018 publication in the European Respiratory Journal (Marsh et al. ERJ 2018).

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Figure 1: Principal component analysis of historical flow cytometry data from the LBI-LVR, reveals strong inflammatory changes in different lung compartments.

To further develop our research portfolio, Leigh Marsh performed a short-term scientific mission to the laboratory Ed Morrisey at the Perelman School of Medicine, University of Pennsylvania. Here, Leigh Marsh spent two weeks learning the intricacies of single cell RNAI11 analysis. This knowledge is essential for supporting several projects by analysis existing open access datasets.



Figure 2: Single cell RNA sequencing (scSRNAseq) analysis of the open access dataset (GSE129605), including feature map overlays of smooth muscle actin (Acta2), CD45 and surfactant protein C (Stfpc).

All these new techniques continue to support the institute's molecular and clinical arms. Deeper analysis of our pre-clinical models will allow better characterisation of the involvement of specific genes and molecules, and their contribution to disease pathogenesis.

Research Cooperations

GRUNIG Gabriele Dr, New York University School of Medicine, New York, USA GRILLARI Johannes Prof, Ludwig Boltzmann Institute for Experimental and Clinical Traumatology HEINEMANN Akos Prof, Otto Loewi Research Centre, Medical University of Graz, Austria STROBL Herbert Prof, Otto Loewi Research Centre, Medical University of Graz, Austria

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2.3 Clinical Studies



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Project overview and main research results

The main aim of the clinical arm of the LBI is to promote the early diagnosis of chronic pulmonary vascular diseases. Based on our recent data, mild hemodynamic changes at rest and an abnormal hemodynamic reaction of the pulmonary circulation during exercise may suggest the presence of early pulmonary vascular disease. In 2019 we aimed to further understand these conditions. In addition we continued to utilize and to improve our non-invasive fully automated computed tomography algorithm to assess the characteristics of the pulmonary vessels and their associations with functional indices in different pathologic conditions. Below, the most important developments of these areas are discussed in more detail.

Clinical Research Collaboration - Pulmonary Hemodynamics during Exercise Research Network (PEX-NET)

The assessment of pulmonary hemodynamics during exercise provides important clinical information in patients with respiratory and cardiac diseases. Alterations may represent early forms of pulmonary vascular diseases or latent pulmonary and cardiac dysfunction. Based on an ERS Task Force expert statement (Kovacs et al. ERJ 2017) highly important scientific questions have been recently identified in this field including the prognostic relevance of pulmonary hemodynamics during exercise and its added

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value to the assessment of resting hemodynamics. With these main objectives this ERS Clinical Research Collaboration (CRC) was established in 2017. The CRC is coordinated by clinical researchers of the Medical University of Graz and of the LBI. The CRC aims for retrospective as well as prospective analysis of pulmonary hemodynamics during exercise by using a web-based electronic database. Since its initiation, the CRC established, tested, released and adapted the database. In 2019 the number of participating centers and included patients increased significantly. Currently 37 international centers from 15 countries have joined the project and data of more than 550 patients have already been included. The inclusion of further patients is ongoing and it appears realistic that by the end of 2020 we reach the number of planned patients (n>1000). This project is currently the largest multicenter study worldwide to investigate the prognostic relevance of pulmonary hemodynamics during exercise. In order to continue with prospective recruitment, the ERS recently prolonged the funding of the CRC until 2023. The generated data will likely provide sufficient evidence for the re-introduction of a definition for exercise pulmonary hypertension in future Pulmonary Hypertension Guidelines and may stimulate further diagnostic and therapy studies in the field of early pulmonary vascular disease.

The clinical relevance of mildly increased pulmonary arterial pressure

In 2019, researchers of the Clinical Arm of the LBI together with world-wide known experts on pulmonary vascular diseases summarized the existing evidence on the clinical relevance of mildly increased pulmonary arterial pressure.

Recent robust epidemiological data from numerous populations worldwide, including an important clinical study from the LBI (Douschan et al. AJRCCM 2018) have clearly demonstrated that mean pulmonary arterial pressure (mPAP) exceeding 19 mmHg is prognostically relevant. Modifying the approach to capturing pulmonary hypertension (PH) patients early has important implications on risk stratification, clinical trial design, and the management of patients. This recognition also led to lowering the mPAP threshold in the suggested hemodynamic definition of PH according to the Proceedings of the 6th World Symposium on Pulmonary Hypertension. In this new definition, pre-capillary PH is defined by mPAP > 20 mmHg, pulmonary arterial wedge pressure of \leq 15 mmHg and a pulmonary vascular resistance of \geq 3 WU. The change in the hemodynamic definitions of PH has raised several questions regarding the causes, the clinical relevance and the optimal management of mildly elevated mPAP.

The major reasons, which alone or in combination, explain a mild mPAP increase in most subjects, are shown in Figure 1 and include left heart diseases, lung diseases and early pulmonary vascular disease, defined here as pulmonary vascular remodeling with hemodynamic consequences occurring in the absence of left heart or lung disease.

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The above considerations provide a basis for further clinical research and currently ongoing projects of the LBI address mildly impaired pulmonary hemodynamics in all these conditions. Patients with early pulmonary vascular disease are of specific interest since even in the contemporary era, patients with pulmonary arterial hypertension are frequently recognized in a late stage although early diagnosis of the disease may lead to earlier initiation of specific therapy and better outcome.



Figure 1: Conceptual representation of the estimated relative frequency of patients with underlying pulmonary, cardiac and pulmonary vascular diseases and presenting with normal or increased mean pulmonary arterial pressures. Adapted from Kovacs G et al. Eur J Heart Fail. (2019)

Lung vessel morphology

In order to examine how the lung vessel morphology changes in chronic lung diseases with potential vascular involvement, we applied our in-house developed fully-automatic algorithm for artery/vein separation and analysis to thoracic computed tomography (CT) images from international cohorts with idiopathic pulmonary fibrosis (IPF), chronic obstructive pulmonary disease (COPD) and systemic sclerosis.

In the study on vascular changes in IPF, we were able to show that the vessel volume, normalized to the lung volume, correlated with several of the relevant clinical parameters used in the diagnosis of these patients. One hallmark of IPF is the large variability in the disease progression. While in some patients the disease progresses only gradually and very slow, others show a fast progression and die soon after diagnosis. Currently, there are no clinical parameters available that can reliably distinguish these patients. In this regard, we found that the normalized vessel volume was able to distinguish patients with higher or lower probability to die. While in the tertile with the highest normalized vessel volume

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about 50% of the patients died within 2 years, in the tertile with the lowest values less than 10% died in the same period. Thus, this parameter is a promising readout to stratify these groups and, therefore, enable decisions on how aggressive a treatment shall be. These results have been published in Respirology (2019) 24:445 and presented at the 2019 annual congress of the American Thoracic Society as well as the LBG Health Science meeting in November 2018.

Further, we currently analyse lung vessel morphology in cooperation with the German COSYCONET. This is a large cohort of 600 patients with COPD, who underwent detailed examinations over several years. The study on vascular changes in Systemic sclerosis is carried out in cooperation with the University of Florence, which hosts a renowned centre treating these patients. Preliminary results from these studies also show correlations of morphologic readouts with relevant clinical parameters.

While we can analyse the morphology of pulmonary arteries and veins in great detail from thoracic CT images, we currently omit the structure of the heart, which is always visible in the images and is known to yield further valuable readouts for the evaluation of the respective patient. Therefore, we are currently working to change this by developing a machine learning algorithm that can fully-automatically identify the cardiac structures. A first version was tested on chest X-ray images and already showed promising results. These were presented at the conference on Medical Image Computing and Computer Assisted Interventions (MICCAI) in 2019 and the conference paper was published in Lecture Notes in Computer Science (2019) 11768:664.



Figure 2: Heart segmentation from thoracic computed tomography images using fully-automatic machine learning algorithm: a) axial view with right atrium (dark blue), right ventricle (blue), left atrium (dark red) left ventricle (red) and left myocardium (green); b) 3D rendering of the heart shown from posterior additionally showing the main pulmonary artery (light blue) and the aorta (orange).

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Scientific Cooperations

AVIAN Alexander, Mag. Medical University of Graz, Austria BERGHOLD Andrea, Prof. Medical University of Graz, Austria BRODMANN Marianne, Prof. Medical University of Graz, Austria CONDLIFFE Robin, Prof. Sheffield University, England GRANINGER Winfried, Prof. Medical University of Graz, Austria D'ALTO Michele, Prof. University of Campania, Neaples, Italy DUMITRESCU Daniel, Dr. University of Cologne, Germany FUCHSJÄGER Michael, Prof. Medical University of Graz, Austria HAFNER Franz, Prof. Medical University of Graz, Austria HERMANN Josef, Prov.Doc. Medical University of Graz, Austria HORWATH-WINTER Jutta, Priv.Doc. Medical University of Graz, Austria JACOB Joseph, Dr. Royal Brompton Hospital, United Kingdom JOBST Bertram, Dr. Heidelberg University Hospital, Germany LANGE Tobias Dr. University Clinic Regensburg, Germany LAWRIE Allan, Prof. Sheffield University, England MAIER Robert, Prof Medical University of Graz, Austria MARON Bradley, Prof. Harvard Medical School, Boston, USA MOAZEDI-Fürst Florentine, Dr. Medical University Graz, Austria MORRELL Nicholas, Prof. Cambridge University, Great Britain MÜLLER Veronika, Prof. Semmelweis University Budapest, Hungary NAEIJE Robert, Prof. Free University of Brussels, Belgium OCCIPINTI Mariaelena, Dr. University of Florence, Italy ODLER Balazs, Dr. Medical University of Graz, Austria RAGGAM Reinhard, Dr. Medical University of Graz, Austria REITER Ursula, Dr. Medical University of Graz, Austria SCHLENKE Peter Prof. Medical University of Graz, Austria STAUBER Rudolf, Prof. Medical University of Graz, Austria STOLLBERGER Rudolf, Prof. University of Technology Graz, Austria TORNYOS Adrienn, Dr. Medical University of Graz, Austria ULRICH Silvia, Prof. University of Zurich, Switzerland URSCHLER Martin, Dr. LBI for Clinic Forensic Imaging, Austria

2.4 Publications of the LBI-LVR 2019

Starting in 2010 when our institute was first founded, the cumulative impact factor, an indicator for the quality of our scientific publications with LBI-LVR affiliation, reached the remarkable value of 1317 by the end of the year 2019.



2.4.1 Top five publications 2019 (in alphabetical order)

Birnhuber A, Crnkovic S, Biasin V, Marsh LM, Odler B, Sahu-Osen A, Stacher-Priehse E, **Brcic L**, Schneider F, Cikes N, Ghanim B, Klepetko W, Graninger W, Allanore Y, Eferl R, **Olschewski A, Olschewski H, Kwapiszewska G.** IL-1 receptor blockade skews inflammation towards Th2 in a mouse model of systemic sclerosis. Eur Respir J. 2019 Sep 29;54(3). pii: 1900154. IF 11.807

Crnkovic S, Egemnazarov B, Damico R, Marsh LM, Nagy BM, Douschan P, Atsina K, Kolb TM, Mathai SC, Hooper JE, Ghanim B, Klepetko W, Fruhwald F, Lassner D, Olschewski A, Olschewski H, Hassoun PM, Kwapiszewska G. Disconnect between Fibrotic Response and Right Ventricular Dysfunction. Am J Respir Crit Care Med. 2019 Jun 15;199(12):1550-1560. IF 16.494

Kovacs G, Douschan P, Maron BA, Condliffe R, **Olschewski H.** Mildly increased pulmonary arterial pressure: a new disease entity or just a marker of poor prognosis? Eur J Heart Fail. 2019 Sep;21(9):1057-1061. Epub 2019 Aug 13. IF 13.965

Kwapiszewska G, Johansen AKZ, Gomez-Arroyo J, Voelkel NF. Role of the Aryl Hydrocarbon Receptor/ARNT/Cytochrome P450 System in Pulmonary Vascular Diseases. Circ Res. 2019 Jul 19;125(3):356-366. Epub 2019 Jun 26. IF 15.862

Papp R, Nagaraj C, Zabini D, Nagy BM, Lengyel M, Maurer DS, Sharma N, Egemnazarov B, Kovacs G, Kwapiszewska G, Marsh LM, Hrzenjak A, Höfler G, Didiasova M, Wygrecka M, Sievers L, Szucs P, Enyedi P, Ghanim B, Klepetko W, Olschewski H, Olschewski A. Targeting TMEM16A to reverse vasoconstriction and remodelling in idiopathic PAH. Eur Respir J. 2019 Apr 25. PMID: 31023847. IF 11.807

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2.4.2 Scientific publications 2019

Bärnthaler T, **Jandl K**, Sill H, Uhl B, Schreiber Y, Grill M, Thomas D, Schicho R, Marsche G, Frank S, Heinemann A, Schuligoi R. Imatinib stimulates prostaglandin E2 and attenuates cytokine release via EP4 receptor activation. J Allergy Clin Immunol. 2019 Feb; 143(2):794-797, IF 14.110

Bärnthaler T, Theiler A, **Zabini D**, Trautmann S, Stacher-Priehse E, Lanz I, Klepetko W, Sinn K, Flick H, Scheidl S, Thomas D, **Olschewski H**, **Kwapiszewska G**, Schuligoi R, Heinemann A. Inhibiting eicosanoid degradation exerts antifibrotic effects in a pulmonary fibrosis mouse model and human tissue. J Allergy Clin Immunol. 2019 Dec 5. pii: S0091-6749(19)31625-2. doi: 10.1016/j.jaci.2019.11.032. [Epub ahead of print] PMID: 31812575, IF 14.110

Birnhuber A, Biasin V, Schnoegl D, Marsh LM, Kwapiszewska G. Transcription factor Fra-2 and its emerging role in matrix deposition, proliferation and inflammation in chronic lung diseases. Cell Signal. 2019 Aug 29;64:109408. IF 3.388

Birnhuber A, Crnkovic S, Biasin V, Marsh LM, Odler B, Sahu-Osen A, Stacher-Priehse E, Brcic L, Schneider F, Cikes N, Ghanim B, Klepetko W, Graninger W, Allanore Y, Eferl R, Olschewski A, Olschewski H, Kwapiszewska G. IL-1 receptor blockade skews inflammation towards Th2 in a mouse model of systemic sclerosis. Eur Respir J. 2019 Sep 29;54(3). pii: 1900154. IF 11.807

Bonheur S, Štern D, Payer C, **Pienn M**, **Olschewski H**, Urschler M. Matwo-CapsNet: A Multi-label Semantic Segmentation Capsules Network, in Medical Image Computing and Computer Assisted Intervention — MICCAI 2019: 22nd International Conference, Shenzhen, China, October 13–17, 2019, Proceedings, Part V, D. Shen et al., Editors. 2019, Springer International Publishing: Cham. Lecture Notes in Computer Science, Vol. 11768, p. 664-672., IF 0,60

Canepa M, Franssen FME, **Olschewski H**, Lainscak M, Böhm M, Tavazzi L, Rosenkranz S. Diagnostic and Therapeutic Gaps in Patients With Heart Failure and Chronic Obstructive Pulmonary Disease. JACC Heart Fail. 2019 Oct;7(10):823-833. Epub 2019 Sep 11. IF 8.910

Crnkovic S, Egemnazarov B, Damico R, Marsh LM, Nagy BM, Douschan P, Atsina K, Kolb TM, Mathai SC, Hooper JE, Ghanim B, Klepetko W, Fruhwald F, Lassner D, Olschewski A, Olschewski H, Hassoun PM, Kwapiszewska G. Disconnect between Fibrotic Response and Right Ventricular Dysfunction. Am J Respir Crit Care Med. 2019 Jun 15;199(12):1550-1560. IF 16.494

Egemnazarov B, **Kwapiszewska G**, **Marsh LM**. Echocardiographic Measurement of Right Ventricular Diastolic Parameters in Mouse. J Vis Exp. 2019 Apr 27;(146). IF 0.66

Ewert R, Ittermann T, Habedank D, Held M, Lange TJ, Halank M, Winkler J, Gläser S, **Olschewski H, Kovacs G**. Prognostic value of cardiopulmonary exercise testing in patients with systemic sclerosis. BMC Pulm Med. 2019 Nov 29;19(1):230. doi: 10.1186/s12890-019-1003-7. PMID: 31783745

Foris V, Brcic L, Douschan P, Kovacs G, Stacher-Priehse E, **Olschewski H**. EXPRESS: Advanced interstitial lung fibrosis with emphysema and pulmonary hypertension with no evidence for interstitial lung disease on high resolution CT. Pulm Circ. 2019 Feb 7:2045894019832214. IF 2.283

Grasmann G, Smolle E, **Olschewski H**, Leithner K. Gluconeogenesis in cancer cells - Repurposing of a starvation-induced metabolic pathway? Biochim Biophys Acta Rev Cancer. 2019 May 30; 1872(1):24-36. IF 6.887

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Grünig E, Eichstaedt C, Barberà JA, Benjamin N, Blanco I, Bossone E, Cittadini A, Coghlan G, Corris P, D'Alto M, D'Andrea A, Delcroix M, de Man F, Gaine S, Ghio S, Gibbs S, Gumbiene L, Howard LS, Johnson M, Jurevičienė E, Kiely DG, **Kovacs G**, MacKenzie A, Marra AM, McCaffrey N, McCaughey P, Naeije R, **Olschewski H**, Pepke-Zaba J, Reis A, Santos M, Saxer S, Tulloh RM, Ulrich S, Vonk Noordegraaf A, Peacock AJ. ERS statement on exercise training and rehabilitation in patients with severe chronic pulmonary hypertension. Eur Respir J. 2019 Feb 28;53(2). pii: 1800332. Print 2019 Feb. IF 11.807

Hodgson J, Swietlik EM, Salmon RM, Hadinnapola C, Nikolic I, Wharton J, Guo J, Liley J, Haimel M, Bleda M, Southgate L, Machado RD, Martin JM, Treacy CM, Yates K, Daugherty LC, Shamardina O, Whitehorn D, Holden S, Bogaard HJ, Church C, Coghlan G, Condliffe R, Corris PA, Danesino C, Eyries M, Gall H, Ghio S, Ghofrani HA, Gibbs JSR, Girerd B, Houweling AC, Howard L, Humbert M, Kiely DG, Kovacs G, Lawrie A, MacKenzie Ross RV, Moledina S, Montani D, **Olschewski A, Olschewski H**, Ouwehand WH, Peacock AJ, Pepke-Zaba J, Prokopenko I, Rhodes CJ, Scelsi L, Seeger W, Soubrier F, Suntharalingam J, Toshner MR, Trembath RC, Vonk Noordegraaf A, Wort SJ, Wilkins MR, Yu PB, Li W, Gräf S, Upton PD, Morrell NW. Characterization of GDF2 Mutations and Levels of BMP9 and BMP10 in Pulmonary Arterial Hypertension. Am J Respir Crit Care Med. 2019 Oct 29. doi: 10.1164/rccm.201906-11410C. [Epub ahead of print] PMID: 31661308

Humbert M, Guignabert C, Bonnet S, Dorfmüller P, Klinger JR, Nicolls MR, **Olschewski AJ**, Pullamsetti SS, Schermuly RT, Stenmark KR, Rabinovitch M. Pathology and pathobiology of pulmonary hypertension: state of the art and research perspectives. Eur Respir J. 2019 Jan 24;53(1). pii: 1801887. Print 2019 Jan. IF 11.807

Jacob J, **Pienn M**, Payer C, Urschler M, Kokosi M, Devaraj A, Wells AU, **Olschewski H**. Quantitative CTderived vessel metrics in idiopathic pulmonary fibrosis: A structure-function study. Respirology. 2019 May;24(5):445-452. Epub 2019 Feb 20. IF 4.756

Jandl K, Thekkekara Puthenparampil H, Marsh LM, Hoffmann J, Wilhelm J, Veith C, Sinn K, Klepetko W, Olschewski H, Olschewski A, Brock M, Kwapiszewska G. Long non-coding RNAs influence the transcriptome in pulmonary arterial hypertension: the role of PAXIP1-AS1. J Pathol. 2019 Mar;247(3):357-370. Epub 2019 Jan 16. IF 5.942

Kheirollahi V, Wasnick RM, **Biasin V**, Vazquez-Armendariz AI, Chu X, Moiseenko A, Weiss A, Wilhelm J, Zhang JS, **Kwapiszewska G**, Herold S, Schermuly RT, Mari B, Li X, Seeger W, Günther A, Bellusci S, El Agha E. Metformin induces lipogenic differentiation in myofibroblasts to reverse lung fibrosis. Nat Commun. 2019 Jul 5;10(1):2987. IF 11.878

Kiely D, Levin D, Hassoun P, Ivy DD, Jone PN, Bwika J, Kawut SM, Lordan J, Lungu A, Mazurek J, Moledina S, **Olschewski H**, Peacock A, Puri GD, Rahaghi F, Schafer M, Schiebler M, Screaton N, Tawhai M, Van Beek EJ, Vonk-Noordegraaf A, Vanderpool RR, Wort J, Zhao L, Wild J, Vogel-Claussen J, Swift A. EXPRESS: Statement on imaging and pulmonary hypertension from the Pulmonary Vascular Research Institute (PVRI). Pulm Circ. 2019 Mar 18:2045894019841990. IF 2.283

Kovacs G, **Douschan P**, Maron BA, Condliffe R, **Olschewski H**. Mildly increased pulmonary arterial pressure: a new disease entity or just a marker of poor prognosis? Eur J Heart Fail. 2019 Sep;21(9):1057-1061. Epub 2019 Aug 13. IF 13.965

Kovacs G, Olschewski H. Debating the new haemodynamic definition of pulmonary hypertension: much ado about nothing? Eur Respir J. 2019 Aug 22;54(2). pii: 1901278. Print 2019 Aug. IF 11.807

- 37 —

Kovacs G, Olschewski H. Take your drug and climb Machu Picchu! Int J Cardiol. 2019 Feb 28. pii: S0167-5273(19)30210-4. IF 3.471

Kovacs G, Herve P, **Olschewski H**; PEX-NET Clinical Research Collaboration. The pulmonary haemodynamics during exercise - research network (PEX-NET) ERS Clinical Research Collaboration: investigating the prognostic relevance of exercise haemodynamics. Eur Respir J. 2019 Apr 11;53(4). pii: 1900458. Print 2019 Apr. IF 11.807

Kwapiszewska G, Johansen AKZ, Gomez-Arroyo J, Voelkel NF. Role of the Aryl Hydrocarbon Receptor/ARNT/Cytochrome P450 System in Pulmonary Vascular Diseases. Circ Res. 2019 Jul 19;125(3):356-366. Epub 2019 Jun 26. IF 15.862

Marsh LM, Kwapiszewska G. Lessons from Transcriptomics in Hypoxia-induced Pulmonary Hypertension: Does the Mouse Strain Matter? Am J Respir Cell Mol Biol. 2019 Jan;60(1):13-15. IF 3.79

Merkel OM, **Marsh LM**, Garn H, Kissel T. Flow Cytometry-Based Cell Type-Specific Assessment of Target Regulation by Pulmonary siRNA Delivery. Methods Mol Biol. 2019;1943:365-375. IF 0.38

Mohan T, **Nagaraj C**, **Nagy BM**, Bračič M, Maver U, **Olschewski A**, Stana Kleinschek K, Kargl R. Nano- and Micropatterned Polycaprolactone Cellulose Composite Surfaces with Tunable Protein Adsorption, Fibrin Clot Formation, and Endothelial Cellular Response. Biomacromolecules. 2019 Jun 10;20(6):2327-2337. Epub 2019 May 29. IF 5.667

Nathan SD, Barbera JA, Gaine SP, Harari S, Martinez FJ, **Olschewski H**, Olsson KM, Peacock AJ, Pepke-Zaba J, Provencher S, Weissmann N, Seeger W. Pulmonary hypertension in chronic lung disease and hypoxia. Eur Respir J. 2019 Jan 24;53(1). pii: 1801914. Print 2019 Jan. IF 11.807

Olschewski H, Canepa M, **Kovacs G**. Pulmonary and cardiac drugs: clinically relevant interactions. Herz. 2019 Jul 11. IF 0.995

Papp R, Nagaraj C, Zabini D, Nagy BM, Lengyel M, Maurer DS, Sharma N, Egemnazarov B, Kovacs G, Kwapiszewska G, Marsh LM, Hrzenjak A, Höfler G, Didiasova M, Wygrecka M, Sievers L, Szucs P, Enyedi P, Ghanim B, Klepetko W, Olschewski H, Olschewski A. Targeting TMEM16A to reverse vasoconstriction and remodelling in idiopathic PAH. Eur Respir J. 2019 Apr 25. PMID: 31023847. IF 11.807

Rosenkranz S, Diller GP, Dumitrescu D, Ewert R, Ghofrani HA, Grünig E, Halank M, Held M, Kaemmerer H, Klose H, **Kovacs G**, Konstantinides S, Lang IM, Lange TJ, Leuchte H, Mayer E, **Olschewski A**, **Olschewski** H, Olsson KM, Opitz C, Schermuly RT, Seeger W, Wilkens H, Hoeper MM. [Hemodynamic Definition of Pulmonary Hypertension: Commentary on the Proposed Change by the 6th World Symposium on Pulmonary Hypertension]. Dtsch Med Wochenschr. 2019 Jul 5. IF 0.635

Schnieder J, Mamazhakypov A, **Birnhuber A**, Wilhelm J, **Kwapiszewska G**, Ruppert C, Markart P, Wujak L, Rubio K, Barreto G, Schaefer L, Wygrecka M. Loss of LRP1 promotes acquisition of contractilemyofibroblast phenotype and release of active TGF-β1 from ECM stores. Matrix Biol. 2019 Dec 11. pii: S0945-053X(19)30399-3. doi: 10.1016/j.matbio.2019.12.001. PMID: 31841706 IF 6.986

Seidl C, Panzitt K, Bertsch A, Brcic L, Schein S, Mack M, Leithner K, Prinz F, **Olschewski H**, Kornmueller K, **Hrzenjak A**. MicroRNA-182-5p regulates hedgehog signaling pathway and chemosensitivity of cisplatinresistant lung adenocarcinoma cells via targeting GLI2. Cancer Lett. 2020 Jan 28;469:266-276. doi: 10.1016/j.canlet.2019.10.044. Epub 2019 Nov 5. PMID: 31697978 IF: 6.508

38 —

Smolle E, Leithner K, **Olschewski H.** Oncogene addiction and tumor mutational burden in non-small-cell lung cancer: Clinical significance and limitations. Thorac Cancer. 2019 Dec 4. doi: 10.1111/1759-7714.13246. [Epub ahead of print] Review. PMID: 31799812 IF: 2.524

Spiekerkoetter E, Goncharova EA, Guignabert C, Stenmark K, **Kwapiszewska G**, Rabinovitch M, Voelkel N, Bogaard HJ, Graham B, Pullamsetti SS, Kuebler WM. Hot topics in the mechanisms of pulmonary arterial hypertension disease: cancer-like pathobiology, the role of the adventitia, systemic involvement, and right ventricular failure. Pulm Circ. 2019 Nov 20;9(4):2045894019889775. doi: 10.1177/2045894019889775. eCollection 2019 Oct-Dec. PMID: 31798835 IF: 2,283

Theiler A, Bärnthaler T, Platzer W, Richtig G, Peinhaupt M, Rittchen S, Kargl J, Ulven T, **Marsh LM**, Marsche G, Schuligoi R, Sturm EM, Heinemann A. Butyrate ameliorates allergic airway inflammation by limiting eosinophil trafficking and survival. Methods Mol Biol. 2019 May 11. pii: S0091-6749(19)30613-X. IF 0.38

Weiss A, Boehm M, **Egemnazarov B**, Grimminger F, Pullamsetti SS, **Kwapiszewska G**, Schermuly RT. Kinases as potential targets for treatment of pulmonary hypertension and right ventricular dysfunction. Br J Pharmacol. 2019 Nov 10. doi: 10.1111/bph.14919. [Epub ahead of print] Review. PMID: 31709514 IF: 6.583

Zucker MM, Wujak L, **Gungl A**, Didiasova M, Kosanovic D, Petrovic A, Klepetko W, Schermuly RT, **Kwapiszewska G**, Schaefer L, Wygrecka M. LRP1 promotes synthetic phenotype of pulmonary artery smooth muscle cells in pulmonary hypertension. Biochim Biophys Acta Mol Basis Dis. 2019 Mar 22. pii: S0925-4439(19)30086-9. IF 4.328

3 Cooperation with our Partners

For this year's annual report we have organized two statements from our partners, Caroline Schober-Trummler of the Medical University of Graz and Heidrun Dorsch, Alliance Manager of Bayer AG. Questions about the supporting activities and the benefits from the cooperation were asked.

3.1 Statement by Heidrun Dorsch



The statutes/expectations of the Ludwig Boltzmann society that partners from science, industry and the public sector should cooperate, are fully met at the Ludwig Boltzmann Institute (LBI) for Lung Vascular Research by the cooperation of researchers at the institute, physicians from the Medical University of Graz and scientists from Bayer. When partners from different fields, in this case basic biological research, clinical research and industrial drug research come together,

things can get complicated and require a certain degree of coordination. A few years ago, Bayer therefore set up a new department to coordinate cooperations with academic and other partners. The employees of this department call themselves "Alliance Managers".

Since 2011, Heidrun Dorsch has been the Alliance Manager for Bayer and part of the management board of the LBI for Lung Vascular Research. On behalf of Bayer AG, we received the following feedback from Heidrun Dorsch on the collaboration and the importance of the cooperation with the LBI for Lung Vascular Research.

Cooperation of the Bayer AG and the LBI for Lung Vascular Research

Bayer considers the cooperation with the LBI for Lung Vascular Research as a strategically important collaboration for early research to develop new drugs for lung diseases such as pulmonary hypertension. Since the foundation of the LBI for Lung Vascular Research in 2010, we have worked together on several projects that were promising for drug development at Bayer. Some of the results of this collaboration have been described in patent applications that Bayer has submitted to the international patent offices for examination. We hope that important impulses and suggestions for new targets will continue to emerge from this collaboration as starting points for future drug development.

3.2 Statement by Caroline Schober-Trummler



Caroline Schober-Trummler studied chemistry at the Karl-Franzens-University of Graz and turned her scientific attention to biochemistry and molecular biology. However, her heart has always beaten not only for science, but also for management. As a marketing and change management consultant, she worked on projects in the USA and China in the field of industrial minerals. Combining both passions, she managed numerous national and international large-scale research

projects before she became manager of the Institute for Molecular Biosciences at the Karl-Franzens-University of Graz from 2011 to 2016. Since February 2016 Caroline Schober-Trummler has been Vice Rector for Research and International Affairs at the Medical University of Graz. Her second term of office started at the beginning of this year.

Cooperation of the Medical University of Graz and the LBI for Lung Vascular Research

Caroline Schober-Trummler likes to emphasize the importance of the cooperation between the Ludwig Boltzmann Institute (LBI) for Lung Vascular Research and the Medical University of Graz. The LBI has not only found a home in terms of space since its foundation at the Medical University (since 2019 even in the new, ultra-modern premises of the Med Campus), its tight collaboration also allows to bridge basic and clinical research and application, and therefore builds the key to the success of common research projects. The image of the lonely researcher in an ivory tower has ceased to exist; rather, close local, national and international networking has become a basic requirement for being able to gain creative solutions and profound insights. The LBI has also become a valued and important cooperation partner within the university - numerous joint project proposals paint a clear picture here. In this way, new, interdisciplinary research approaches can be found and implemented together. The requirements for special equipment and the corresponding specialist expertise are also increasing - here the cooperation between LBI and the core facilities of the Medical University of Graz with its large equipment and research-supporting services has proven very successful. Human sample material collected by the LBI for research purposes is safely stored in the Biobank of the Medical University of Graz according to the highest international quality standards and smooth sample logistics are guaranteed. The Medical University of Graz supports the LBI not only by providing space, personnel and in kind contributions, but also by continuous high financial support. The aim is to establish a long-term successful and internationally highly competitive research area, which will continue to have strong university ties even after the funding by the Ludwig Boltzmann Society expires, and to raise substantial funds to continue research in the field of pulmonary hypertension and other lung diseases.

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4 Teaching and Training Activities of the Institute

4.1 Training in the LBI for Lung Vascular Research

4.1.1 Training of the LBI-LVR Staff

Following advanced trainings and congresses were visited in 2019:

Name	Location	Title of the Lecture/ Workshop	
BIRNHUBER Anna	Medical University of Graz, Austria	Spezifische Weichenstellung für	
		Postdocs (Ute Riedler)	
BIRNHUBER Anna	LBG Career Center, Vienna, Austria	Stressabbau durch die L.A.C.H	
		Methode – mehr Heiterkeit im	
		Business (Nina Fuchs-Bittmann)	
BIASIN Valentina	Medical University of Graz, Austria	Basic Module Teaching: Testing - did	
		the knowledge transfer take place	
		appropriately? - Overview of	
		examination formats	
BIASIN Valentina	Medical University of Graz, Austria	Basic Module Research: Research at	
		the Med Uni Graz	
BIASIN Valentina	MUG Graz, LBI LVR, OIS of the LBG	CO-CREATION WORKSHOP; CoNNECT	
		Open Innovation Project	
FORIS Vasile	Medical University of Graz, Austria	Master of Science Biobanking (2018-	
		2020), master program	
JANDL Katharina	LBG career center	Stressmanagement	
MUTGAN Ayse Ceren	Medical University of Graz, Austria	ia PhD Seminar on Complementary Skill	
		Biostatistics and R	
MUTGAN Ayse Ceren	Medical University of Graz, Austria	Proteomics	
MUTGAN Ayse Ceren	Medical University of Graz, Austria	Flow Cytometry, Basic Course	
NAGY Bence	LBG, Vienna, Austria	Co-create Careers Circle	
NAGY Bence	Medical University of Graz, Austria	Introduction for R software for Life	
		Sciences	
NAGY Bence	Medical University of Graz, Austria	Advanced R software for Life Sciences	
NAGY Bence	LBG, Vienna, Austria	Public and Patient Involvement and	
		Engagement (PPIE) Program	
		workshops/meetings	
KWAPSIZEWSKA	LBG, Vienna, Austria	Open Innovation in Science	
Grazyna			
KWAPSIZEWSKA	LBG, Vienna, Austria	Leadership summit meeting LBG	
Grazyna			
MARSH Leigh	University of Pennsylvania, USA	scRNA analysis using R	

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NAGY Bence	Florenz, Italy	Keystone Symposium	
OLSCHEWSKI Andrea	Deutscher Hochschulverband	Dekane und ihre Leitungsaufgaben	
OLSCHEWSKI Andrea	London Schoool of Economics and	Managementausbildung: Executive	
	Political	MSc in Health economics, policy and	
		management	
PIENN Michael	Medical University of Graz, Austria	PH bei Lungen-/Herzerkrankungen	
PIENN Michael	ÖGP	Rechtsherzechokardiographie-Kurs	
PIENN Michael	LBG Career Center, Vienna, Austria	Stressmanagement	
PIENN Michael	Medical University of Graz, Austria	Einblicke in den Lungenhochdruck für	
		Radiologen	
SASSMANN Teresa	Medical University of Graz, Austria	Grundlagen für	
		Medizinerinnen/Mediziner	
ZABINI Diana	Medical University of Graz, Austria	Quadrilateral Physiology Symposium	
		2019	
ZABINI Diana	Medical University of Graz, Austria	Basismodul Lehre_Abschlussarbeiten	
		von Idee zur Realisierung	
ZABINI Diana	Medical University of Graz, Austria	Basismodul Lehre_Beurteilungen von	
		Abschlussarbeiten	
ZABINI Diana	Medical University of Graz, Austria	Basismodul Lehre_Einführung in die	
		Hochschuldidaktik SS2018	
ZABINI Diana	Medical University of Graz, Austria	Basismodul Lehre_Evaluierung_wir	
		wollen besser werden SS2018 (1st)	
ZABINI Diana	Medical University of Graz, Austria	Basismodul Lehre_Hochschuldidaktik	
		Lehr und Lehrmethoden	
ZABINI Diana	Medical University of Graz, Austria	BASISMODUL Lehre_Prüfen erfolgte	
		der Wissenstransfer zweckmäßig_	
		Uberblick Prüfungsformate	
ZABINI Diana	Medical University of Graz, Austria	Basismodul Lehre_Prüfen_erfolgte de	
		Wissenstransfer zweckmaßig	
		(2)_technische Unterstutzung	
ZABINI Diana	Medical University of Graz, Austria	Basismodul Lenre_Prufen_erroigte der	
		choice Fragen \$22018 (2)	
	Modical University of Graz Austria	Pasismodul John Urboharracht und	
	Wedical Oniversity of Graz, Austria	Datepschutz	
7ABINI Diana	Medical University of Graz Austria	Basismodul Lehre: Patientinnen	
		stehen im Mittelnunkt der klinischen	
		lehre	
ZABINI Diana	Medical University of Graz Austria	Basismodul Forschung an der	
		MeduniGraz Abläufe und	
		Ansprechpartnerinnen	
ZABINI Diana	Medical University of Graz. Austria	Einführung neuer Mitarbeiterinnen	

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4.1.2 Invited Speakers 2019

BRADLEY A.Maron, MD	Harvard Medical School, Cardiovascular Medicine, Brigham and Women's Hospital, USA	29 JAN 19	Using artificial intelligence to clarify exercise intolerance phenotypes
GRILLARI Johannes, MD	Institute for Molecular Biotechnology, BOKU Vienna, Austria	12 FEB 19	From cell senescence to biomarkers of age associated disease
GUIGNABERT Christophe, PhD	Univ Paris Sud - Université Paris Saclay, Hôpital Marie Lannelongue, France	11 MAR 19	Pericyte in Pulmonary Hypertension
BRISLINGER Dagmar, PhD	Divison of Cell Biology, Histology and Embryology, Gottfried Schatz Research Center for Cell Signaling, Metabolism and Aging, Medical University of Graz, Austria	09 APR 19	3D cell culture models for vessels
KLEPETKO Walter, MD	Medical University of Vienna, AKH Vienna - Vienna General Hospital, Austria	30 APR 19	Lung Transplantation
GROSCHNER Klaus, MD	Division of Biophysics at the Gottfried-Schatz-Research Center of the Medical University of Graz, Austria	07 MAY 19	Optically controlled probe to identify lipid-gating fenestrations within the TRPC channels
ZHAO Youyang, PhD	Northwestern University Feinberg School of Medicine, USA	15 JUL 19	Targeting endothelial dysfunctional for treatment of pulmonary arterial hypertension: Role of PHD2/HIF-2a signaling
WAGNER Erwin, PhD	Clinical Department of Dermatology, Medical University of Vienna, Austria	10 SEP 19	Innate immune signalling in Inflammatory Skin/Joint Disease and Lung Fibrosis
ZIRLIK Andreas, MD	Clinical Department of Cardiology, Medical University of Graz, Austria	22 OCT 19	Inflammatory mechanisms in atherosclerosis

TELLO Khodr, PhD	UKGM (University Hospital Giessen and Marburg), Justus-Liebig-University Giessen, Germany	03 DEC 19	Methoden zur Erfassung der rechtsventrikulären Kontraktilität
SCHERMULY Ralph, MD	UKGM (University Hospital Giessen and Marburg), Justus-Liebig-University Giessen, Germany	17 DEC 19	Antiproliferative drugs for treatment of pulmonary hypertension