ANNUAL REPORT
2010

Ludwig Boltzmann Institute
Lung Vascular Research

Ludwig Boltzmann Institute for Lung Vascular Research

1. The Institute in overview

The Ludwig Boltzmann Institute for Lung Vascular Research (LBI-LVR) was founded in July 2010.

1.1 Aims

Pulmonary hypertension (PH) is a chronic, prolonged crippling and fatal disease. Progressive loss of exercise capacity and suffering from dyspnoea represent the most threatening features for the individuals affected by this sickness. Clinical care for PH is currently extremely costly and prolonged, 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 affected individuals, but are far away from curing the disease or providing a substantially prolonged lifespan or a good quality of life. The Ludwig Boltzmann Institute for Lung Vascular Research aims to provide a significant contribution to early recognition of the disease via novel and non-invasive methods, the development of new pathology-based therapies, and the prevention of disease progression to the stage where highly costly therapies are necessary, thus prolonging life expectancy and improving health and quality of life.

1.2 The Institute in numbers

The budget of the newly established institute is app. 8.7 million Euro for the first four years. The Ludwig Boltzmann Society covers 55% of the total costs. The remaining 45% of the cost is shared by the consortium of our partners.

1.3 Partners of the Institute

We thank our Partners, all members of the Ludwig Boltzmann Society and the managing committee and the Government of Austria for continuous support.

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

The Ludwig Boltzmann Gesellschaft, our most important Partner, is a private sponsor of research establishments in Austria.

Medical University of Graz (http://www.medunigraz.at/)

The Medical University of Graz (MUG) has declared strategically 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 spectrum in 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 nucleus 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/)

Pulmonary hypertension is one of the main focus-points for Bayer Health Care (BHC). BHC is currently developing new therapeutic options for the treatment of pulmonary hypertension, like the soluble guanylate cyclase stimulator Riociguat. 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 and associated pathological changes and conditions in pulmonary hypertension.

Nebu-tec (http://www.nebu-tec.de/)

Nebu-Tec GmbH was established with the primary focus to develop and manufacture inhalation devices for the treatment of pulmonary hypertension. In addition to clinical and patient treatment, Nebu-Tec devices are used by different biotechnology companies in research. The strategic interest of Nebu-Tec for the participation in the LBI is to further develop a relevant and realistic market of intrapulmonary delivery of targeted PH drugs via specialized inhalation devices.

Austrian Academy of Sciences (http://www.oeaw.ac.at/)

The Austrian Academy of Sciences (OEAW) is the leading non-university research institution in Austria. It is the core-scope of the OEAW to participate in national and international scientific research programmes. The OEAW is represented by the

Institute of Biophysics and Nanosystems Research (IBN). The partnership with the LBI will extend existing knowledge and expertise concerning the development of lipid-based pulmonary delivery systems.

1.4. Boards

Advisory Board of the Partners (Board)

Mag. Claudia Lingner (Ludwig Boltzmann Gesellschaft)

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

PD Dr. Hubert Trübel (Bayer Health Care)

Stefan Kern (Nebu-Tec)

Prof. Dr. Georg Stingl (Austrian Academy of Sciences, OEAW)

Scientific Advisory Board (SAB)

Prof. Ada Yonath –Weizmann Institute of Science

Prof. Steve Abman – University of Colorado

Prof. Wolfgang Kuebler – University of Toronto,
Heart Institute of Berlin

Prof. Jose Lopez-Barneo – University of Sevilla

Prof. Dean Sheppard – University of California

The first annual meeting with evaluation of the scientific work via the Board and SAB members together with all scientists of the LBI-LVR is planned for October 2011.

1.5. Personal and human resources development

Every PhD or postdoctoral fellow has an individual project and each group has scientific independence in generating their individual progress.

Group members

Program line A (PLA):

Dr. Grazyna Kwapiszewska-Marsh (Program line leader)

Valentina Biasin MSc. (Researcher /PhD student)

Slaven Crnkovic MSc. (Researcher /associated PhD student through the scientific cooperation with the MUG)

Ass. Prof. Dr. Andelko Hrzenjak (Researcher /associated scientist through the scientific cooperation with the MUG)

Chandran Nagaraj MSc. (Researcher /associated PhD student through the scientific cooperation with the MUG)

Univ. Prof. Dr. Andrea Olschewski (Researcher)

Dr. Elvira Stacher (Researcher)
Julia Schittl (Technician)
Elisabeth Wirnsperger (Technician)
Diana Zabini MSc. (Researcher /associated PhD student through the scientific cooperation with the MUG)

Dr. Grazyna Kwapiszewska-Marsh overtook a position in LBI as a group leader of PLA in November 2010. Her initial aim as the group leader was establishing and organising the new laboratory space of the LBI. From January 2011 the laboratory has been fully equipped and general molecular biology methods established.

Valentine Biasin is as a PhD student of the Molecular Medicine doctoral programme at the MUG since October 2010. She is supervised by Dr. Grazyna Kwapiszewska-Marsh. Her primary goal is to decipher novel candidate genes involved in PH development.

Slaven Crnkovic is a third year PhD student of the Molecular Medicine doctoral programme at the MUG. He is supervised by Prof. Andrea Olschewski through the scientific cooperation with the MUG. His research focus is the vascular remodelling in chronic hypoxia-induced pulmonary hypertension.

Dr. Andelko Hrzenjak is an assistant professor in the Department of Pulmonology at the MUG. He supports the institute in field of proteomics since September 2010.

Chandran Nagaraj is a fourth year PhD student of the Molecular Medicine doctoral programme at the MUG and supervised by Prof. Andrea Olschewski. His research focus is the regulation of ion channel function in human pulmonary arteries.

Dr. Andrea Olschewski's primary focus is on ion channels and their modulation in the pulmonary circulation.

Dr. Elvira Stacher joined the institute as a pathologist in September 2010. She supports the institute in different issues regarding the histology of human and animal lungs.

Julia Schittl joined the group in December 2010 as a technical assistant. In addition to general laboratory organisation she supports Dr. Grazyna Kwapiszewska-Marsh in performing laboratory work.

Elisabeth Wirnsperger joined the group in September 2010 as a part-time technical assistant. She is responsible for the preparation of cells from human pulmonary arteries.

Diana Zabini is a second year PhD student of the Molecular Medicine doctoral programme at the MUG and supervised by Dr. Andrea Olschewski. Her research focus is vascular remodelling in chronic thromboembolic pulmonary hypertension.

Program line B (PLB):

Dr. Leigh Marsh (Program line leader)
Peter Blümel MSc. (Technician)
Adina Friedl (Technician)
Pritesh Jain MSc. (Researcher /PhD student)
Dr. Dipl.-Ing. Regina Leber (Researcher)
Univ. Doz. Dr. Ruth Prassl (Supporting scientist)
Stefanie Tamegger MSc. (Technician)
Hui Xu MSc. (Researcher /associated PhD student through the scientific cooperation with the MUG)

Program line B1

Since January 2011 Dr. Leigh Marsh has headed the PLB work group. His main roles have been the establishment and expansion of the PLB team and instruction of the new employees in molecular biological techniques in the centre for medical research (ZMF) at the MUG. Additionally, he has planed the experimental procedures required for the establishment of an inflammatory model of pulmonary hypertension.

Peter Blümmel supports the institute part-time and is experienced in the isolated perfused lung model. He is currently instructing fellow PLB members on this technique.

Stefanie Tamegger is a new technical assistant employed since January 2011. She is currently learning the isolated perfused lung model and in charge of cell culture facilities and laboratory organisation.

Hui Xu is a recently recruited PhD student who is a member of Molecular Medicine doctoral programme at the MUG and supervised by Dr. Leigh Marsh. She is currently training in animal handling, tissue harvesting and preservation techniques.

Program line B2

Dr. Ruth Prassl is principal investigator and working group leader at the Institute of Biophysics and Nanosystems Research (IBN) of the Austrian Academy of Sciences (OEAW). Her scientific contribution (OEAW in kind) to the research program of the LBI focuses on the development of nanoparticulate aerosol drug formulations. She is responsible for the accomplishment of tasks within the scheduled timescale, organisation, management, training, data evaluation and timely dissemination of results, all within the area of nanoparticle formulations and nebulisation thereof.

Dr. Regina Leber is employed as senior scientist since September 2010 and is responsible for the development of stable drug nanocarriers for controlled released pulmonary therapy. She is currently instructing the PhD student and the biomedical engineer in lipid-based drug carrier preparation methods and biophysical techniques. Her responsibilities include the planning and coordination of experiments performed by the B2 team concerning drug-carrier formulations, nebulisation of drug carriers, as well as the in vitro and in vivo test systems.

Jain Pritesh is a recently recruited PhD student and a member of the Molecular Medicine doctoral programme at the MUG. He is currently being trained in liposome research, nanoparticle formulation and characterisation methods, and how to apply biophysical techniques and perform data analysis. He is supervised by Prof. Ruth Prassl.

Adina Friedl is employed as biomedical engineer at the LBI and working at the IBN. Her responsibilities include routine laboratory work, sample preparation, analytical procedures and biophysical measurements.

Program line C (PLC):

Dr. Zoltán Bálint (Program line leader)

Michael Pienn (PhD student)

Dr. Zoltán Bálint has led PLC since September 2010. His responsibilities include the planning and coordination of experiments performed by PLC in the development of a quantitative, non-invasive and reproducible technique with minimal user intervention for hemodynamic assessment of the pulmonary circulation by means of chest computed tomography imaging.

Michael Pienn joined the institute in October 2010 as a PhD student. His main duty is to set-up the protocol for dynamic assessment of pulmonary circulation as well as computed tomography image analysis. He constructs and tests on a phantom a dual-energy computed tomography protocol for dynamic data acquisition, analyzes the phantom data. He is supervised by Dr. Zoltan Balint and Prof. Rudolf Stollberger.

Program line D (PLD):

Dr. Gabor Kovacs (Program line leader)
Dr. Vasile Foris (PhD student)
Helen Höller (Study nurse)
Univ. Prof. Dr. Horst Olschewski (Supporting scientist)
Dr. Maria Tscherner (Researcher)

Dr. Gabor Kovacs is the program line leader of the PLD. He trains Dr. Tscherner, Dr. Foris and Mrs. Höller to perform the necessary clinical examinations used in the studies of PLD (right heart catheterisation, echocardiography, exercise echocardiography, cardiopulmonary exercise test). His main responsibility to plan and initiate the clinical studies (impedance cardiography, rebreathing method for measurement of cardiac output, standardization of exercise tests, exercise Doppler echocardiography, and follow-up of borderline PH).

Dr. Vasile Foris is a PhD student of the Molecular Medicine doctoral programme at the MUG since October 2010: His major interest on biomarkers in PH. He is supervised by Dr. Gabor Kovacs.

Helene Höller is study nurse in PLD. She assists at the different examinations used in PH and actively is involved in the establishment of the integrative database.

Prof. Dr. Horst Olschewski is the leader of the Department for Pulmonology at the Medical University of Graz. He supports the PLD to plan clinical studies and coordinates research with the other program lines of the LBI.

Dr. Maria Tscherner is a physician in the PLD and responsible for invasive and non-invasive testing and their evaluation.

1.6 Infrastructure

The LBI for Lung Vascular Research is predominately located at the Center for Medical Research (ZMF) at the MUG, which supports the LBI with cutting-edge research facilities guaranteeing high-yield development of this field. The aerosol studies are performed at the research facilities of the Austrian Academy of Sciences, Institute of Biophysics and Nanosystem Research (IBN) in Graz. The clinical research group of the PL D is hosted by the Division of Pulmonology at the University Hospital of the MUG.

1.8 Public relations

There are four compelling reasons to believe that pulmonary hypertension will become an increasingly important burden on the population and for healthcare providers.

1) Although, the 4th World Conference on Pulmonary Hypertension in Dana Point (2008) defined PAH with pulmonary arterial pressure (PAP) values above 25 mmHg, this designation was not fully evidence-based. According to more recent published epidemiological data on pulmonary pressures in healthy controls at rest and exercise, the average mean PAP is 14.0 mmHg with a 3.3 mmHg standard deviation. Therefore values above 20.6 could more reasonably be considered to be elevated. Assuming a normal PAP distribution within the population, the number of PH patients would increase 400-fold if the definition would be changed from 25 to 20.6 mmHg.

2) Currently 80% of all PAH cases are diagnosed in the late stages. If awareness and screening technology would be more available, this number could be decreased to 30%, dramatically increasing the number of patients awaiting therapy.

3) Targeted therapies are efficacious but their effects are modest and mainly palliative. They are not able to normalize pulmonary haemodynamics. Although current therapies may retard the progression of the disease, no convincing evidence has been found that they improve survival. Therefore it is necessary to development of new therapies that address mechanisms intrinsic to the pathology of pulmonary hypertension. New and innovative application of drugs and new diagnostic tools is obvious and of high interest.

4) The vast majority of PH patients belong to the non-PAH-PH group (for example PH with interstitial lung disease (ILD) or PH with chronic obstructive pulmonary disease (COPD)). There is not only a high unmet medical need for targeted PH medications in these groups, but also at this point in time a limited understanding of underlying pathomechanisms and possible therapeutic avenues.

To improve the awareness of the society for the disease the Institute closely collaborates with the "Austrian pulmonary hypertension self-help association" (www.lungenhochdruck.at/) in order to 1) Plan joint activities with patients, 2) Create central information points and 3) Provide comprehensive information for patients and relatives. Our first joint activity is the “Blaue Lippe – Aktionstag”.

2. Research content 2010

2.1 Research projects

The 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 four program lines (PLA-D).

As the research projects of the Institute are carried out on human and animal tissues and also include human studies, all projects must be approved by the Ethical committee or by the Austrian Federal Ministry for Science and Research (animal studies). The first research projects have already been approved by the Ethical Committee of the MUG and the Medical University of Vienna.

PROGRAM LINE A – Leader: Dr. Grazyna Kwapiszewska-Marsh

Pathomechanisms of vascular remodelling - reverse-remodelling strategies

Program line A is divided into two thematic areas:

Area A1: Novel signalling pathways contributing to the development of human pulmonary hypertension

Area A2: Analysis of expression and function of ion channels and regulators of calcium homeostasis in PH

Group members

Valentina Biasin MSc. (PhD student)
Slaven Crnkovic MSc. (Associated PhD student through the scientific cooperation with the MUG)
Ass. Prof. Dr. Andelko Hrzenjak (Researcher)
Dr. Grazyna Kwapiszewska (Program line leader)
Chandran Nagaraj MSc. (Associated PhD student through the scientific cooperation with the MUG)
Univ. Prof. Dr. Andrea Olschewski (Researcher)
Julia Schittl (Technician)
Dr. Elvira Stacher (Researcher)
Elisabeth Wirnsperger (Technician)
Diana Zabini MSc. (Associated PhD student through the scientific cooperation with the MUG)

Research projects

Area A1: Novel signalling pathways contributing to the development of human pulmonary hypertension

Our group focuses on the identification of novel molecular targets to better understand the signalling pathways that lead to vascular remodelling during the development of pulmonary arterial hypertension (PAH) and possible therapeutic interventions. The primary goal is the establishment of human tissue bank that will contain the samples from IPAH (idiopathic pulmonary arterial hypertension) as well as non-PAH PH patients suffering from lung diseases like COPD or ILD as well as a tissue bank of different animal models.

The identification of novel targets will be achieved by applying microarray technology on laser-microdissected vessels from patient lungs. Emphasis will be made on discovering genes that may be involved in vascular remodelling in PH. These studies will be extended with investigations on candidate genes and proteins, protein-translocations and structural changes using state-of-the art technologies. In addition, full-genome sequencing systems (next generation sequencing) and linkage studies are available if appropriate. The functional role of the verified pathways will be further investigated in combination with PLB using experimental PH models.

Additionally, work has been done to establish hypoxia-induced pulmonary hypertension in mice. This is of great importance as hypoxia mice develop right heart hypertrophy and vascular remodelling which partially mimic pulmonary hypertension in humans. Moreover, mice are the best tools to investigate function of gene candidates due to easy accessibility to knock-out animals.

Area A2: Analysis of expression and function of ion channels and regulators of calcium homeostasis in PH

It is frequently stated in the literature that the down-regulation of voltage-gated potassium (K^+) channels in pulmonary artery smooth muscle cells (PASMC) leads to increased proliferation and thus contributes to vascular remodelling in PH. Although this concept has become the dogma in the PH community over the last ten years, it is noteworthy that this common pathologic mechanism in PH is only poorly documented. Therefore there is a compelling need for a robust validation of this observation. In addition, rescuing of K^+ or other ion channel activity may represent an important therapeutic target for reverse remodelling and thus PH. For these

investigations, methods are routinely applied in the PLA will be extended with studies on intracellular calcium homeostasis (live cell Ca^{2+}-imaging method), membrane potential (patch-clamp), proliferation and apoptosis assays.

The first project collaborates closely with Prof. Walter Klepetko and Prof. Irene Lang from the Medical University of Vienna as well as with Dr. Zoltán Bálint, the leader of PLC. The focus is the *chronic thromboembolic pulmonary hypertension (CTEPH)*. CTEPH is a rare and late possible consequence of venous thromboembolism. This study investigates the potential contribution of chemokines for angioneogenesis in occluded pulmonary arteries and pulmonary vascular remodeling of CTEPH patients.

The second project focuses on the *signalling pathway of prostacyclin*. This project collaborates with Prof. Phil Aaronson at the King's College London, UK. Prostacyclin analogs form an important pillar of modern therapy of peripheral arteriovascular diseases as well as pulmonary hypertension. Prostacyclin released in the pulmonary circulation acts via IP receptors leading to activation of adenylate cylase and finally to vasodilation. However, the molecular mechanisms of the vasodilating effects of prostacyclin in human pulmonary artery are poorly understood. We have recently demonstrated that the prostacyclin analog treprostinil activates the so called background potassium (K+) channel TASK-1 at clinically relevant concentrations. Our present data show that clinically relevant concentrations of two prostacyclin analogs activate both calcium-dependent K+ channel (K_{Ca}) and TASK-1 in primary human pulmonary artery via IP receptors. The activation of K_{Ca} and TASK-1 led to a hyperpolarization of the membrane potential in human pulmonary artery smooth muscle cells consistent with vascular relaxation. These results were supported by genetic silencing of the channels and by pharmacological inhibition.

The third projects deals with the *regulation of K^+ channel function in human pulmonary arteries in physiological conditions as well as in PH*. Here we closely collaborate with Prof. Ken Weir from the University of Minnepolis, USA.

PROGRAM LINE B (PLB) – Leader: Dr. Leigh Marsh

Pharmacologic tailoring and assessment

Program line B is divided into two thematic areas:

Area B1: Experimental models of pulmonary hypertension

Area B2: Establishment of drug delivery systems for aerosolic application

Group members

Dr. Leigh Marsh (Program line leader)

Peter Blümel, MSc. (Technician)

Adina Friedl (Technician)

Pritesh Jain MSc. (PhD student)

Dr. Regina Leber (Researcher)

Prof. Dr. Ruth Prassl (Supporting scientist)

Stefanie Tamegger, MSc (Technician)

Hui Xu MSc. (associated PhD student through the scientific cooperation with the MUG)

Research projects

Area B1: Experimental models of pulmonary hypertension

Development and characterisation of an inflammatory model of pulmonary hypertension

To establish inflammation based remodelling, mice will be exposed to a crude extract of the allergen house dust mite (HDM). Inhalation of HDM induces experimental asthma and is associated with strong inflammatory cell recruitment and pronounced airway remodelling. Additionally prolonged HDM exposure leads to remodelling of the intrapulmonary vessels. Following ethics committee approval, animal experiments will be undertaken to establish the time course of vessel remodelling by challenging mice with HDM. Consequently, time points will be identified which can be used to investigate the initiation and also full establishment of pulmonary vascular remodelling. The model will be analysed by both physiological (haemodynamics, right heart hypertrophy and pulmonary vascular remodelling) and molecular techniques (real-time PCR, immunohistochemistry and flow cytometry).

Expression and function of chemokines and their receptors in the pathophysiology of PH

Established models of experimental pulmonary hypertension (hypoxia + Sugene treated rats and allergen sensitized and challenged mouse model) will be examined

for expression of cytokines and chemokines (e.g. MCP-1, MIP-1a, CCL3, fractalkine/CX3CL1, SDF-1/CXCR4 and RANTES) on mRNA and protein levels. The effects of chemokine/chemokine receptor antagonists on experimental pulmonary hypertension will be then examined. Analysis will be by haemodynamics, right heart hypertrophy and pulmonary vascular remodelling in experimental PH. In addition, for further characterisation gene knockout mice will be used.

Area B2: Establishment of drug delivery systems for aerosolic application

Design, development and biophysical characterisation of liposomes/micelles

Lipid-based nanocarriers will be developed for controlled release. Within the first six months of the PLB2 we have started to prepare the first generation of loaded liposomes. Multilamellar, unilamellar and sterically stabilized liposomes were formulated and characterized by photon correlation spectroscopy in terms of size and polydispersity. Since the project is potentially bound to patenting it is not described in detail.

Development of reliable inhalation devices combined with nanoparticle delivery systems for animal models of PH and for PH patients

Three different types of inhaler, air-jet, vibrating mesh and ultrasonic (latter was provided in kind of LBI partner NebuTec.) were chosen to compare the aerosol behavior of liposome model drug formulations using a mechanical, electronically-controlled lung simulation device (in kind contribution of NebuTec). Initial tests to verify the integrity of nebulized liposomes have been successfully performed.

PROGRAM LINE B (PLC) – Leader: Dr. Zoltán Bálint

Technical development of innovative non-invasive diagnostics of PH

Group members

Dr. Zoltán Bálint (Program line leader)

Michael Pienn (PhD student)

Research projects

The aim of PLC is to provide a quantitative, non-invasive and reproducible technique with minimal user intervention for hemodynamic assessment of the pulmonary circulation by means of chest computed tomography (CT) imaging.

Algorithm development for pulmonary perfusion

To develop a new algorithm and software accessing regional perfusion parameters of the lung, first a dual-energy CT (DECT) acquisition protocol will be established with the help of phantom experiments performed on static and dynamic phantoms. This project collaborates PD Dr. Thorsten RC Johnson at Institute for Clinical Radiology, Grosshadern, University of Münich. We have established the phantom measurements using a Siemens Definition Somatom Flash Dual-Energy CT instrument and analyzed for spatial and temporal resolution, as well as for signal-to-noise and contrast-to-noise ratios. The quality control of the gathered data served for the optimization of the detection protocol.

From these data a proposed protocol for pulmonary perfusion visualization has been derived, which is waiting for permission from the Ethical Committee of Medical University of Graz to be tested on patients and healthy volunteers. With the help of this newly established protocol gathering both, static and dynamic information from the pulmonary blood flow is possible.

PROGRAM LINE B (PLD) – Leader: Dr. Gabor Kovacs

Clinical data base and clinical studies

Group members

Dr. Gabor Kovacs (Program line leader)
Dr. Vasile Foris (PhD student)
Helen Höller (Study nurse)
Dr. Maria Tscherner (Researcher)
Prof. Dr. Horst Olschewski (Supporting scientist)

Research projects

This program line contains different subprojects:

Development of an integrative patient database

The establishment of an integrative database is one of the most important tasks of PLD. This will provide easily accessible data from all patients, including complete diagnostic data at all time points for retrospective generation and prospective evaluation of diagnostic and prognostic algorithms. The electronic databank has been expanded retrospectively including all our patients' data gained from right heart catheterizations with pharmacological test or exercise, cardio-pulmonary exercise tests, exercise Doppler echocardiography examinations and resting echocardiography examinations since 2006. The next step will be the import of 6-minute walk tests, ECGs, lung function tests, laboratory tests, the medical history and personal data for all our patients with suspected or verified PH since 2006, as well as their stratification based on their haemodynamics and clinical characteristics.

Clinical biobank, biomarkers

As part of the clinical database, serum, plasma and full blood of patients with PH will be reserved in the Biobank of the MUG. The cooperation between the LBI and the Biobank has been established. The storage of the probes will start after the finalization of the protocol.

Evaluation of innovative non-invasive methods

The evaluation of innovative non-invasive methods has been initiated by using a Commercial Impedance Cardiograph (CNSystems) in combination with invasive right heart catheterization. The preliminary data showed several potential errors of the method in this setting (ideal position of electrodes, achievement of optimal signal and curves, optimal timing of measurements) which need to be addressed. After the optimization of the method, and harmonization with the right heart catheterizations we plan to evaluate the method in a larger study population.

Furthermore we aim to create an algorithm that "corrects" 6mwd for the magnitude of subjective and objective exertion in order to improve the reliability of the test. A pilot study was started in order to show a correlation between the Borg Dyspnea Score and the distance walked during tests performed with different efforts. After evaluating the data, the "standard 6wmd" will be prognostically evaluated and compared with the conventional 6mwd.

Screening and management of patients with early PAH

The LBI continued to perform exercise Doppler echocardiography examinations in patients at risk for PAH (connective tissue disease, myelodysplastic syndrome) to identify early PAH by means of exercise-induced PAP increase. A hemodynamic follow-up study has been initiated in patients with connective tissue disease, who underwent exercise Doppler echocardiography or right heart catheterization previously.

2.4 Scientific Conferences

Olschewski, A: Potassium channels as therapeutic targets for pulmonary hypertension. University Complutense Madrid, Spain; 13.09.2010. Invited lecture

Olschewski, A. Pulmonary hypertension and hypoxia - The role of potassium channels. D-A-CH Meeting on Pulmonary Hypertension; Heidelberg, Germany; 21-23.10.2010

Olschewski, A. Importance of tyrosine kinases for potassium channel function in the human pulmonary artery smooth muscle cells. 10th Cologne Conference; Cologne, Germany; 17-18.09.2010

Olschewski, A. Potenzielle neue Therapieziele bei PAH. Jahrestagung der Österreichischen Gesellschaft für Pulmonologie. Graz; 7-10.10.2010

Olschewski, A. The role of two-pore domain channels (K2P) in smooth muscle cells. Joint Meeting of the Scandinavian and German Physiological Societies; Copenhagen, Denmark; 27-30. 2010. Keynote lecture

Zabini D, Bálint Z, Klepetko W, Lang I, Olschewski H, Olschewski A. Neovascullariztation in clots of chronic thromboembolic pulmonary artery hypertension patients. Wiener Klinische Wochenschrift 2010 nov 122(21-22):A52-A53. Oral presentation

Bálint Z. Harmonized function of parts of the cells. 3rd Transylvanian Free University; Mihaieni, Romania; 21-24.10.2010 Oral presentation

3. Other activities

3.1. Scientific cooperations

Program line A

Prof. Phillip Aaronson, King's College London, London, UK

Prof. Walter Klepetko, Medical University of Vienna, Vienna, Austria

Prof. Irene Lang, Medical University of Vienna, Vienna, Austria

Prof. Rory E. Morty, Max Planck Institute for Heart and Lung Research, Bad Nauheim, Germany

Prof. E. Kenneth Weir, University of Minneapolis, Minnesota, USA

Prof. N. Weissmann, University Giessen Lung Center, Giessen, Germany

Dr. M. Wygrecka, University Giessen Lung Center, Giessen, Germany

Prof. L. Fink, Institute of Pathology and Cytology, UEGP, Wetzlar, Germany

Program line C

Prof. Rudolf Stollberger, Institut für Medizintechnik, Technical University of Graz, Austria

PD Dr. Thorsten Johnson Klinikum der Universität München Klinikum Großhadern, München, Germany

Program line D

Prof. Ekkehard Grünig; Thoraxklinik am Universitätsklinikum Heidelberg; Germany

3.3. Teaching activities

Dr. Andrea Olschewski is involved in teaching at different levels at the Medical University of Graz. She gives student lectures in the Human Medicine Diploma Program (Anaesthesiology, Intensive Care Medicine and Pain therapy), seminars for doctoral studies and by supervision of PhD students: Diana Zabini, Chandran Nagaraj and Slaven Crnkovic. Furthermore she is the supervisor of the PhD students Yingji Li and Patrick Chorlich at the University of Giessen, Germany.

Dr. Grazyna Kwapiszewska-Marsh taught between 2005 and 2010 within the frame of Graduate School "Molecular Biology and Medicine of the Lung" at University Giessen Lung Center. She is currently supervising two PhD students at University Giessen Lung Center, Christine Veith and Friderike Weisel and one PhD Student at LBI-LVR Miss Valentina Biasin.

Dr. Leigh Marsh is currently supervising PhD student Xi Hui.

Dr. Zoltan Balint is currently co-supervising PhD student Michale Pienn.

Dr. Gabor Kovacs is currently supervising PhD student Vasile Foris. In addition, he gives student lectures in the Human Medicine Diploma Program (Pulmonology).

3.4. Internal activities of the Institute

Key researcher meeting

The LBI-LVR key researchers meet every second week to discuss on budget and task distribution, research and various other open issues for the benefit of the institute. A protocol is made in written form accessible to the key researchers for internal organisation.

Weekly laboratory seminars

The LBI-LVR members and associated researchers meet every week at the laboratory seminars, where one or two researchers display their projects with discussion and trouble shooting.

Journal Club seminars

All four program lines of the Institute have a weekly Journal Club seminar, where a topic related paper is presented and discussed. These seminars are implemented into the Ph.D. programme Molecular Medicine of the MUG and several other PhD students have joined this seminar.

Group member meeting

The LBI-LVR members meet every month to discuss issues of the organisation of the institute, task distribution, research and various other open issues. The frequency of these meeting will be adapted to the needs of the institute in the future. We plan to reduce it up to four meetings per year from the next year and in addition to increase social activities integrating every members of the institute.

4. Perspectives and Future outlook

The LBI for Lung Vascular Research is almost fully established at the end of 2010. The research projects will start 2011 according to the timeline of the research program.

5. Publications

Avcuoglu S, Wygrecka M, Marsh LM, Günther A, Seeger W, Weissmann N, Fink L, Morty RE, **Kwapiszewska G**. The TrkB/NT4 Signaling Axis is Perturbed in Clinical and Experimental Pulmonary Fibrosis. Am J Respir Cell Mol Biol. 2011 Feb 17. [Epub ahead of print]

Nikam VS, Schermuly RT, Dumitrascu R, Weissmann N, **Kwapiszewska G**, Morrell N, Klepetko W, Fink L, Seeger W, Voswinckel R. Treprostinil inhibits the recruitment of bone marrow-derived circulating fibrocytes in chronic hypoxic pulmonary hypertension. Eur Respir J. 2010 Dec;36(6):1302-14. Epub 2010 Jun 4.

Hecker M, Zaslona Z, **Kwapiszewska G**, Niess G, Zakrzewicz A, Hergenreider E, Wilhelm J, Marsh LM, Sedding D, Klepetko W, Lohmeyer J, Dimmeler S, Seeger W, Weissmann N, Schermuly RT, Kneidinger N, Eickelberg O, Morty RE. Dysregulation of the IL-13 receptor system: a novel pathomechanism in pulmonary arterial hypertension. Am J Respir Crit Care Med. 2010 Sep 15;182(6):805-18. Epub 2010 Jun 3.