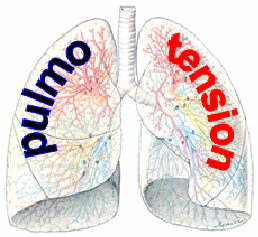

Life Sciences, Genomics and Biotechnology for Health

LSHM-CT-2005-018725

PULMOTENSION

Pulmonary Hypertension: Functional Genomics and Therapy of Lung Vascular Remodelling

Integrated Project

Priority 1: Life Sciences, Genomics, and Biotechnology for Health (LIFESCIHEALTH)

Final Report

Publishable Final Activity Report

Period covered: from 01/01/2009 to 31/12/20089 Date of preparation: 30th August 2010

Start date of project: 01/01/06 Duration: 48 months

Project coordinator: Werner Seeger
Project coordinator organisation: University of Giessen Lung Centre (UGLC)

Draft

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1. Project Execution

Deciphering of the functional genomics of lung vascular remodelling and identification of new molecular targets to alleviate or even cure pulmonary hypertension has been the main objective of this project. To this end, the work of the consortium spans the entire field from basic research to clinical studies.
We have characterised a number of different molecular mechanisms underlying the dramatic remodelling processes in the lung vasculature, which result in an increase in vascular resistance by more than one order of magnitude. To this end, genetics, functional genomics, and proteomics have been combined with cell culture studies, experimental pulmonary hypertension animal models, and analysis of clinical tissue bank material. A survey of PH patients has been conducted covering three major European Centers for disease management, diagnostic tools for non-invasive diagnosis of lung vascular and right heart remodelling are being tested. Finally, based on the identification of new genes and signalling pathways as novel therapeutic targets, preclinical and clinical studies with focus on anti-remodelling treatment have been performed and are still underway. In all aspects, gender differences have been particularly addressed. The members of the Consortium have jointly managed to carry out an ambitious translational research programme, with the intent to perform an analysis "from molecules to patients".
According to the scientific nature of our project, generation of new knowledge and improvement of PH patient therapy have been the primary goals of the Consortium. Publications in international peer-reviewed journals (see 2. Dissemination and Use), patents, evaluation of new diagnostic and therapeutic approaches, standardization of these techniques throughout Europe, and information to society are important measurable objectives in this respect. Due to the strong translational research infrastructure of the Consortium, we expect innovative therapies to become available for patients suffering from PH, as a result of the work of this Consortium. This has already been implemented in two clinical trials conducted within the frame of this Integrated Project and will be further followed based on the results gained during the project´s lifetime.
The objectives also include the promotion of a long-lasting European infrastructure for scientific and technical competence in the field of vascular remodelling and PH. Training and mobility programs, especially for young researchers, mechanisms for technology transfer and educational programs, and are being continued with partners of the consortium.

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Project Outline

Pulmonary hypertension (PH) describes a group of devastating diseases, comprising hereditary, idiopathic and secondary forms, which cause breathlessness and premature death, representing a major burden on healthcare systems. Extensive lung vascular remodelling with loss of vessel patency is *the* underlying pathomechanism in PH.
PULMOTENSION integrates the top European Centres in PH and lung vascular biology in a multidisciplinary approach, with the aim to combat and finally maybe even find a cure for PH. The expertise of all members fully extends from the initial discovery of gene mutations causative of PH to having established new therapeutic regimen of PH.
We have identified and analysed different underlying molecular pathways, identified distinct targets for anti-remodelling therapy, fostered drug development based on these targets, and tested these new treatment options in preclinical and clinical trials.

Concentrating on factors that have been shown to play a major role in the development of Pulmonary Hypertension, we structured our research programme according to these 7 areas.

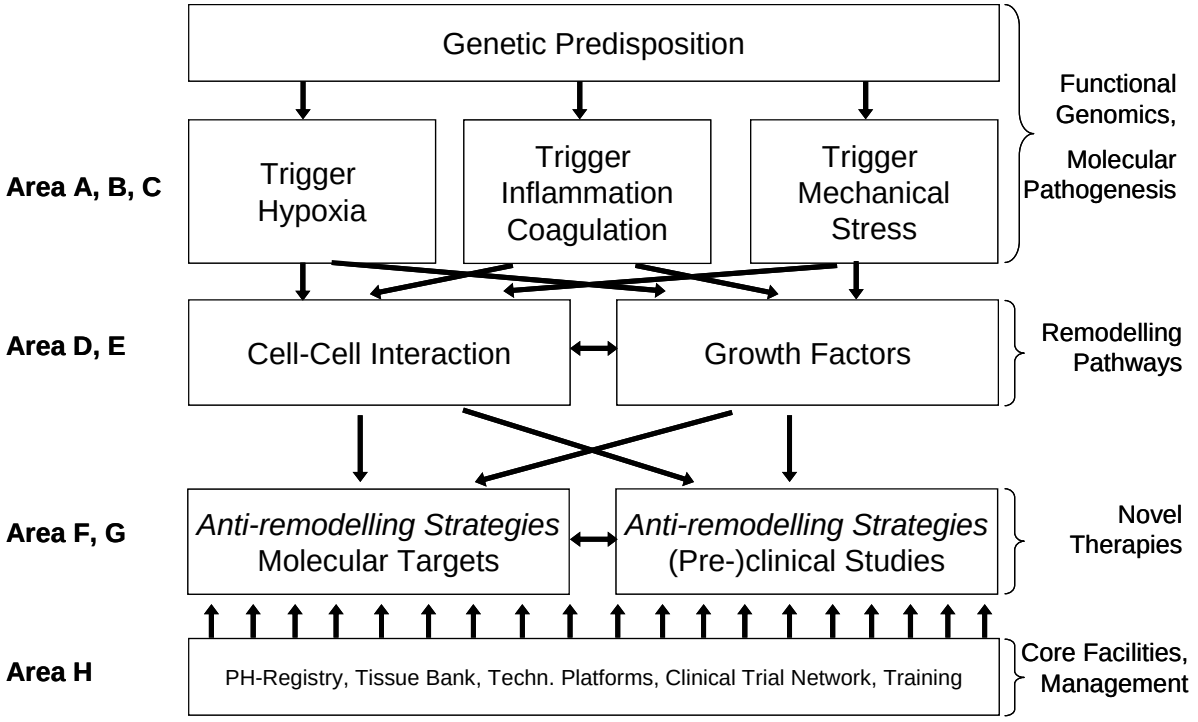

Figure 1: Interrelation of thematic areas and innovation strategy of PULMOTENSION

Area A – Pathomechanisms of Vascular Remodelling – Hypoxia

Reduced oxygen supply affects the expression of genes that regulate vascular tone and proliferation of vascular cells:
At the cellular level we investigated the possible sites for oxygen sensors and the distribution of oxidised/reduced areas in the cells: redox imaging with oxygen-sensitive dyes in living cells. Further, we assessed the impact of hypoxia on the activity of ion channels. Hypoxia-inducible factor (HIF), a transcription factor, and HIF-hydroxylases play an important role in the regulation of gene expression, vascular tone and remodelling, which we further investigated, also with regard to options of modulating this regulation as a possible treatment of PH. Erythropoietin (epo), one of the genes regulated by HIF, has not only erythropoietic, but also anti-pulmonary hypertensive effects. Thus, we

wanted to study this effect in detail, also in relation to other vascular regulatory pathways. The mechanisms leading to vascular remodelling under chronic hypoxia are not fully understood, thus, we studied the effects of hypoxia on gene expression with special regard to the respiratory chain and potassium channels.

Using advanced fluorescence microscopic technologies (FRAT & FRAP) and other optical methods (e.g. 2-photon laser microscopy), we were able to analyse the distribution of HIF-complexes in living cells and to study the transcriptional activity of the HIF-α subunit, its subcellular distribution, migration, and interaction (UDE). In addition to HIF, we found that GDF15, another hypoxia-inducible gene product, is regulated independently of HIF and is regulated by iron and oxygen, thus presenting an intriguing link in the interaction of iron- and oxygen-regulated pathways (UOXF). With respect to epo, we found a dose-dependent up-regulation of NO-production in mouse erythrocytes treated with human epo (UZ), indicating a close interaction with the NOS pathway and possibly explaining the protective effect against pulmonary hypertension. Non-phagocytic NADPH-oxidases (NOX) are known as major players in the regulation of hypertrophy, remodelling and angiogenesis, and are also discussed as oxygen sensors. We found the isoform NOX4 upregulated in hypoxic animal models and also in human IPAH lung tissue. In addition, Fhl-1was identified as a novel protein regulated in PH. It is HIF-dependent and Fhl-1 overexpression increased migration and proliferation (UGLC). The complex of heme-oxygenase-2 and BK channel, known to act as oxygen sensor in the carotid body, however, are not involved in vascular remodelling in response to hypoxia.

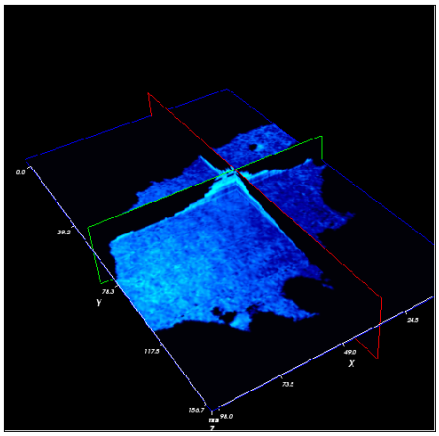

Figure 2: Homogeneous distribution of HSP33 probe throughout the rat pulmonary smooth muscle cell imaged in 3D with new software

Area B – Pathomechanisms of Vascular Remodelling - Inflammation and Coagulation

In a subgroup of PH, chronic thromboembolic pulmonary hypertension (CTEPH), thrombotic (coagulation) processes play an important role, and the development of PH may also be further affected by inflammation, viral infection and auto-immunity processes. We studied inflammatory processes in the context of lung vascular remodelling and the coagulation processes involved. Moreover, the impact of infections on the resolution of thrombi was investigated.

Investigating chemokines in PH, we found that fractalkine induces proliferation of smooth muscle cells and that CCL2 (CC chemokine ligand 2) is upregulated in human IPAH endothelials cells. CCL2 acts as an attractant for circulating inflammatory cells and as a growth factor for pulmonary arterial smooth muscle cells. These findings further support the major role of inflammation in the development/course of PH. Moreover, dendritic cells (known as key players in immunity and tolerance) have been found to be recruited to the lesions of remodeled vessels in PH (HOAB, INSERM). Studying the effects of staphylococcal infection on thrombus resolution in a mouse model, we found that staphylococci delayed the resolution of thrombi and, in addition, growth factor TGF-ß (see also Area E) and connective tissue growth factor were upregulated. A study in a large group of

CTEPH patients revealed a number of risk factors conferring susceptibility to CTEPH: splenectomy, infected pacemakers, and –newly identified- ongoing thyroid hormone replacement therapy and history of malignancy (MUV). Moreover, the two-pore-domain potassium channel TASK-1, maintaining membrane potential in pulmonary arterial smooth muscle cells (PASMC), has been identified to be affected by enothelin-1, causing depolarization (and thus constriction). This may represent a new mechanism contributing to the development of PH (MUG).

Area C – Pathomechanisms of Vascular Remodelling – Mechanical Stress

Mechanical stress in pulmonary vessels occurs due to high blood flow (congenital shunts) or increased blood pressure (increased pulmonary venous pressure leading to distended arterial vessels), this in turn leading to remodelling of the vessels. We have investigated the impact of mechanical stress in in-vitro- and different in-vivo animal models.

One of the factors known to respond to mechanical stress is GDF-15, a member of the TGF-ß cytokine superfamily, currently regarded and utilized as a biomarker in cardiovascular disease. Studies in PH revealed that GDF-15 levels are also increased in PH patients and seem to indicate an increased risk of death or transplantation as a last therapeutic option (MHH). Testing of a selective endothelin receptor-A antagonist, sitaxsentan, in an overcirculation associated PH animal model supports the applicability of sitaxsentan in PH therapy. Analysis of the bone morphogenetic protein (BMP) pathways in PASMC from familial versus idiopathic PH patients revealed differences in BMP receptor downstream signalling (smad/MAPK pathways) (ULB) between these two PH subtypes (see also Area E). Increased vascular pressure may lead to increased vascular permeability (regulated by endothelial cells) and edema formation. Using real-time Ca^{2+} imaging techniques for monitoring endothelial response, we identified a negative feedback loop protecting the microvascular barrier (involving NO and cGMP). Following this line, we have characterized the unique scenario of endothelial dysfunction in congestive heart failure caused by impairment of Ca^{2+} signalling and identified cytoskeletal reorganisation as a major regulator of endothelial signalling and functioning (PhysChar).

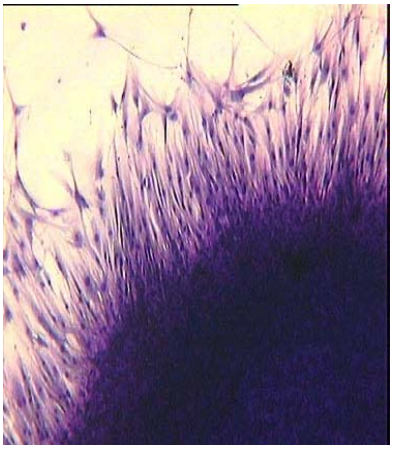

Figure 3: Cellular migration, one of the techniques used in our studies

Area D – Cell-Cell Interaction and Progenitor Cells in Vascular Remodelling

Reports on favourable actions of stem cells in vascular and organ tissue repair have drawn public attention and initial clinical studies for cell based therapy are ongoing (e.g. for cardiac infarction). The role of stem/progenitor cells in PH, on the other hand, is unknown. In particular, it is not clear, either, if circulating progenitor cells (CPC) are indeed favourable or deleterious to the treatment of PH.
Thus we have investigated different bone marrow derived stem cells in murine models (endothelial cells, smooth muscle cells, mesenchymal stem cells), circulating endothelial PCs in animal models and patients, progenitor cells in COPD-induced PH.

We found new expression patterns for flk-1 (fetal liver kinase), which is a receptor for VEGF-A (vascular endothelial growth factor) in lung development, which may be involved in the remodelling process. We also characterized the recruitment of circulating fibrocytes, which show hematopoietic and mesenchymal markers, into the lung in a mouse model of chronic hypoxia. The recruitment of these cells was significantly increased under hypoxia and was affected by the prostacyclin analogue treprostenil (approved therapy for PAH) (UGLC). In studies in patient material and cell cultures we found progenitor cell markers to be elevated in lung tissue from IPAH, familial PAH, and PAH due to congenital heart disease, especially in the remodelled arteries and lesions. Circulating EPC were found to be elevated as well in peripheral blood and these showed a hyperproliferative phenotype in culture and an impaired ability to form vascular networks. This study gives evidence of dysfunctional endothelial progenitor cells in different forms of PAH (UCAM/UGLC). In a collaborative review, the molecular and cellular basis of pulmonary arterial hypertension is summarised and discussed (UCAM/UGLC/INSERM/U of G and other international organisations). Further, working with human cells lines we found evidence for the plasticity of CD133+ cells (circulating peripheral blood cells), showing ability to differentiate into both SMC and EC in co-cultures with these cell types. This was due to a transdifferentiation process and not due to fusion with the co-cultured cells. We have been able to show that EPCs undergo an endothelial-mesenchymal transition process mediated by TGF-ß 1. The proliferation of SMCs has also been found to be present in COPD (model of smoke exposure in guinea pigs), even preceding the development of emphysema (HCPB).

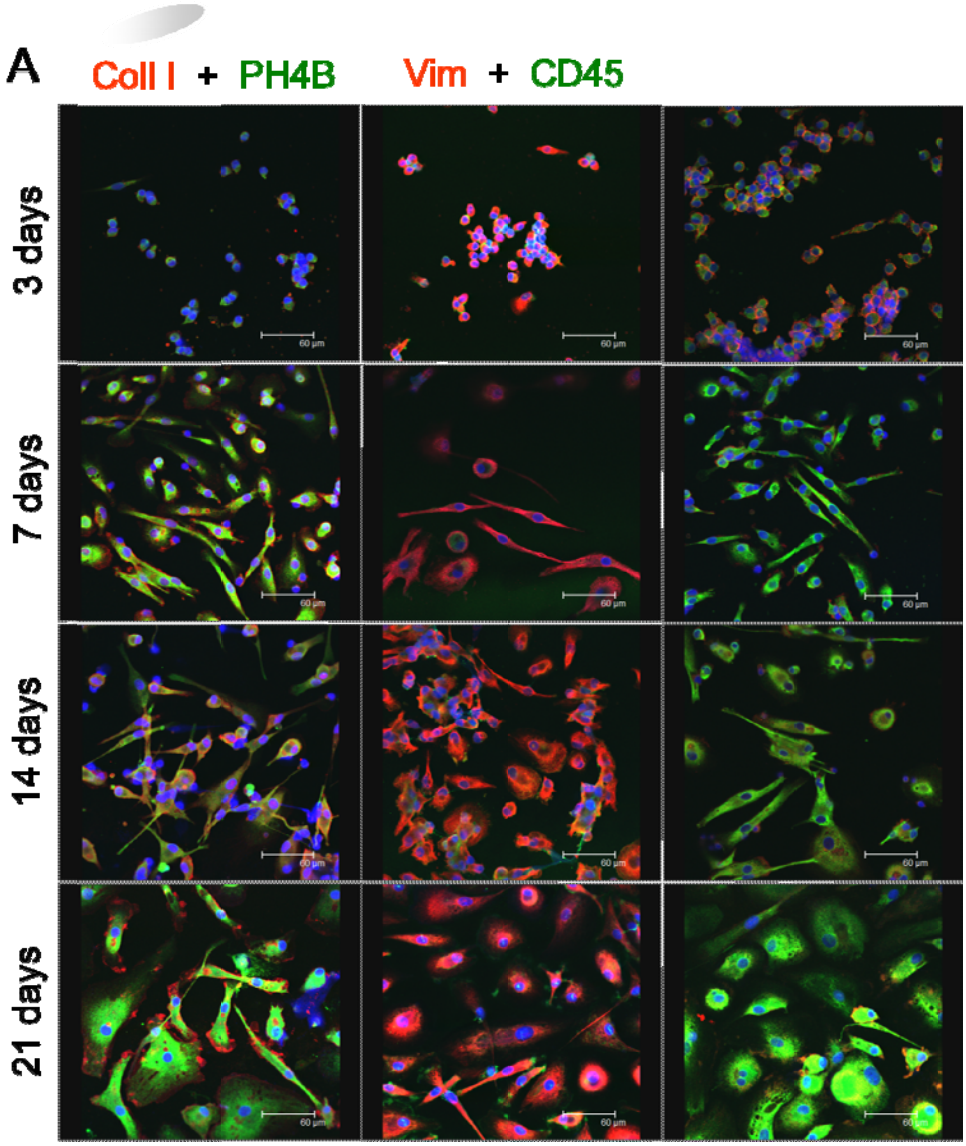

Figure 4: Characterisation and identification of human circulating fibrocytes

Area E - Growth Mediators in Vascular Remodelling

Vascular remodelling can be regarded as result of a complex interplay between stimulators/activators and inhibitors on endothelial and pericyte/smooth muscle cells. We have studied the role of growth factors and mediators in this process, namely: TGF-ß, the serotonin pathway, angiogenetic processes, and membrane trafficking.

Mutations in the Bone Morphogenetic Protein Receptor II (BMPRII) have been shown to cause familial or heritable PAH. Working further on this pathogenetic mechanism we characterized an untranslated 5´ region of BMPRII which leads to premature initiation of translation and RNA decay. This presents a novel mutation of the BMPRII gene working via activation of a cryptic translation site (non-coding site). This finding emphasizes the need for thorough scanning of the entire gene plus non-coding regions when looking at familial cases of PAH. We further identified heme-oxygenase-1 as functional target of BMP4 signalling in human PASMC. Analysing the role of bone morphogenetic protein (BMP) in development, we found BMPRII expression to be most active during phases of intense vasculogenesis. We found BMP2 and 4 to be involved in migration and proliferation of PAECs and dysfunctional BMP signalling to contribute to the pathogenesis of familial PAH. Following the line of BMPRII mutations, we found a dysregulation of Id gene expression in PASMCs with BMPRII mutations (Id=Inhibitors of DNA binding, implying function as transcription factors). Reduced Id gene expression leads to dysfunctional growth suppression via BMP and thus PASMC proliferation (normally BMP inhibits hyperproliferation of PASMC). Another mechanism of disease development in familial PAH is impaired trafficking of BMPRII to the cell surface. We showed that mutant BMPRII may also associate with BMP type I receptors and thus compensate for the dysfunctional type II receptor (UCAM, KCL). Dysregulation of BMP signalling was also found in the widely used monocrotaline animal model of PAH. In a collaborative effort (UGLC and UCSM) at further analysing the BMPRII signalling pathway, we identified RACK-1 as a novel interaction partner of BMPRII in lung tissue from PH patients. RACK-1 acts as a negative regulator for proliferation. Realising the importance of the cytoskeleton (mainly composed of a-smooth muscle actin) for shape and function of SMCs, we identified shroom as a novel binding partner of actin. Hypertrophy and altered actin organisation have been reported as prominent features of PAH, thus we analysed interaction partners of a –smooth muscle actin (SMA) in PASMCs (the key cell type in PAH) and found shroom to be localised in all bronchial and vascular SMCs, similar to the distribution of SMA. Shroom expression was significantly reduced in human PAMCs and in a mouse model of hypoxia-induced PH. Alteration of the cytoskeleton via shroom may contribute to SMC hyperplasia in PAH (UGLC). Having found that serotonin is over-produced in idiopathic pulmonary hypertension (IPAH) and contributes to PASMC hyperplasia, we further investigated this mechanism. We found that that over-expression of the 5-hydroxytryptamine (=serotonin) transporter gene confers PAH and that angiopoietin influences hyperplasia in SMC by activating the Tie2 receptor, leading to the release of endothelial growth factors (like vascular endothelial growth factor=VEGF). In this context we found 4fold higher expression of Tie2 in PECs and PASMCs of IPAH patients (INSERM). Serotonin is produced from tryptophan by the enzyme tryptophan hydroxylase (Tph). Studying the serotonin pathway in Tph knockout mice, we found less severe hypoxia-induced PAH in these animals, concluding that a dysregulation of 5-HT (=serotonin) synthesis is closely linked to a hypoxia-inducible PH phenotype. The effects found in cell cultures can be reproduced in in-vivo animal models. Further investigations into the serotonin pathway revealed a role for RhoA and Rho kinase in human PAH cell cultures (increased activation via trans-amidation by intracellular serotonin). Studying a growth factor released excessively by ECs from IPAH patients, FGF2, in a rat model, we found that siRNA knockdown of FGF2 prevented and nearly reversed experimental PAH. The same was true for a FGF receptor 1 inhibitor, thus suggesting FGF2 as a new target for treatment of PAH (INSERM).
Some time ago, anorexigens based on fenfluramine derivatives were found to cause PH (dexfenfluramine is a substrate for the serotonin transporter SERT) and increased levels of serotonin are thought to be risk factors for development of PH. We found peripheral serotonin to be critical for the development of dexfenfluramine-induced PH and that dexfen and SERT over-expression add up in severity of PH, but that dexfen can also inhibit development of hypoxic PH via SERT and

MAPkinases. In Tph1 k.o. mice we found these animals to be protected against dexfen effects, emphasizing the importance of de novo synthesis of serotonin with regard to dexfen effects. Other SERT substrates that may also be linked to development of PAH are amphetamines and metamphetamines. Novel therapeutic approaches may be SERT inhibitors and 5-HT 1B receptor inhibitors (found to be effective in experimental PH, U of G).
Investigating vascular endothelial growth factor (VEGF) we found auto-regulation of the VEGF proliferation and migration signalling cascade by enhancing the expression of DUSP1 and 5 phosphatases (UOI) and development of PH in caveolin-knock-out mice.

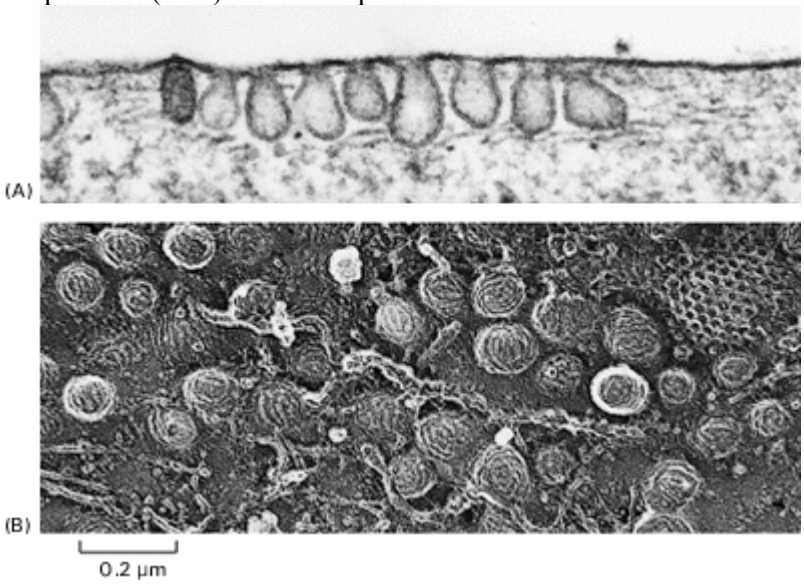

Figure 5: Caveolae are involution of the plasma membrane composed of lipids and proteins, suggested to play a role in transduction of mechanistic (stress) signals

Area F – Anti-remodelling Strategies – Molecular Targets

To find new targets in anti-remodelling we have studied the genetic background of PH (novel genes and modifiers). Recent identification of the biomarker ADMA/DDAH which is elevated in systemic vascular disease prompted us to further study DDAH in the context of PH (pathways and metabolism) and to explore the link to the NOS (NO-synthase) system. In this regard we have also focussed on tetrahydrobiopterin (BH4) as a critical factor of NOS function. The NOS enzyme produces NO which acts as a vasodilator and is mediated via soluble guanylate cyclase (sGC). New therapeutic approaches via manipulation of this system may prove profitable. Thus we have investigated sGC stimulators/activators and their impact on vascular remodelling.

More detailed analysis of the genetic background of PH revealed the involvement even of non-coding regions of the BMPRII gene in the development of PH (see Area E, KCL, UKL-HD). The amino acid "asymmetric dimethylarginine" (ADMA) is a cardiovascular risk factor. ADMA inhibits NO synthase (NOS) and thus formation of NO, a vasorelaxant. DDAH (dimethylarginine dimethylaminohydrolase) is the enzyme that metabolises ADMA, thus having a crucial regulatory function. In a DDAH-1 knock out animal model, loss of DDAH-1 led to a rise in ADMA levels, reduction in NO signalling and vascular pathophysiology: endothelial dysfunction, increased vascular resistance, and elevated systemic and pulmonary blood pressure. ADMA has also been found to be involved in the regulation of cell motility and the actin cytoskeleton, inducing stress fibre and focal adhesion formation and inhibition of cell motility (dependent on RhoA and Rho kinase, see Area E for context with serotonin). This endothelial dysfunction caused by ADMA also leads to impairment of the endothelial barrier function (endothelial leakage). In an experimental trial of adenoviral-mediated overexpression of DDAH, we found that increases of DDAH improves vascular function and compensates long-term exposure to increased ADMA levels. Thus, interventions activating ADMA metabolism (like activation of DDAH) may be of therapeutic use (UCL). Tetrahydrobiopterin (BH4) is a cofactor for

NO synthases (NOS). Studying the effects of BH4 on hypoxic pulmonary vasoconstriction (HPV) in an isolated perfused lung model, we found inhibition of HPV by BH4, concluding that the bioavailability of BH4 is an important determinant of the pulmonary vascular response to hypoxia (ICL), chronic hypoxia being one of the causes of PH. In addition, we investigated another component of the NO signalling pathway, soluble guanylate cyclase (sGC). sGC has been found to be upregulated in IPAH. Stimulating and sensitising sGC with BAY 63-2521, PAH was partially reversed, as well as right ventricular hypertrophy and remodelling (muscularisation of vessels). The sGC activator HMR 1766 elicited acute inhibition of HPV and, under chronic hypoxia, caused reduction of PH, RV hypertrophy and remodelling (UGLC).

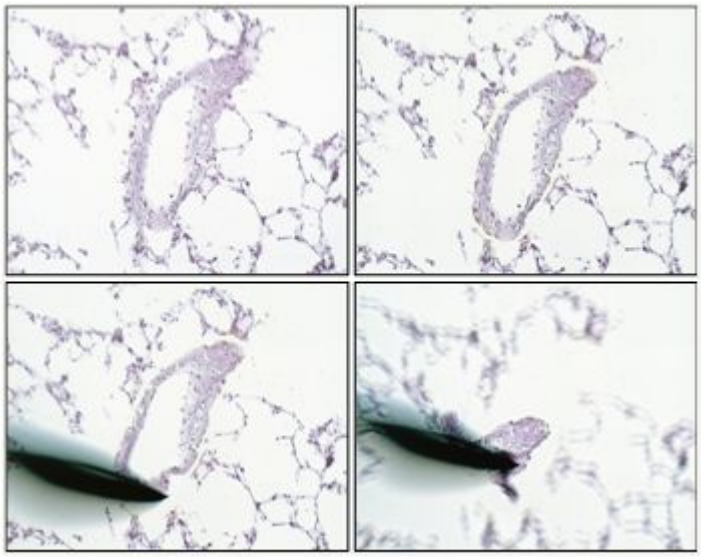

Figure 6: Laser-microdissection, one of the techniques used for analysis of pulmonary micro-vessels.

Area G – Anti-remodelling Strategies – Preclinical and Clinical Studies

As one of the aims of PULMOTENSION is the transfer of our research "from bench to bedside", we have conducted pre-clinical studies with regard to PDE inhibitors, and clinical studies on BH4 (not yet published), and statins, and a diagnostic trial using MRI as a diagnostic tool and for follow-up.
Phosphodiesterases (PDEs) are involved in the metabolism the vasoactive second messengers of prostacyclin (cAMP and cGMP), antagonising contractile signals. Enhanced activity of PDEs has been noted in PAH, thus PDE inhibition seems a feasible target for new PAH therapies. We tested the effects of pumafentrine, a mixed selective PDE 3,4 inhibitor on experimental PH and found a partial reversal of PH, remodelling and right ventricular hypertrophy (UGLC), reflected also by increased cAMP levels and reduction of SMC proliferation. Moreover, we found that by TGF-ß1 stimulation in cell cultures, cAMP levels and PDE4 activity were increased. PDE4 namely, was found to be upregulated in proliferative vascular disease that are associated with epithelial-mesenchymal transition (EMT) processes (see also Area D) like fibrosis, cancer and PAH. Employing rolipram and/or siRNA against PDE4, we found a reduction of EMT-associated changes cell cultures. Overexpression of PDE4 on the other hand elicited reduced levels of epithelial markers, but no change in mesenchymal markers. Investigating PDEs in processe of inflammatory pulmonary diseases, we found inhibitors of PDEs (namely cilomilast by Nycomed) to suppress early inflammatory stages and to attenuate later stages of pulmonary fibrosis. Simvastatin in addition to conventional therapy in a clinical trial showed an early reduction in RV hypertrophy and NT-proBNP (a biomarker of PH), that was, however not sustained over more than 12 months (ICL, UGMLC, UKL-HD). Functional capacity of the right ventricle (RV) of the heart is a major prognostic determinant in PAH, however, no reliable techniques were available until recently for morphology and function imaging. Cardiac magnetic resonance imaging (CMRI) allows both morphological and functional imaging of the RV and the pulmonary circulation (results of study not yet published, SPVU).

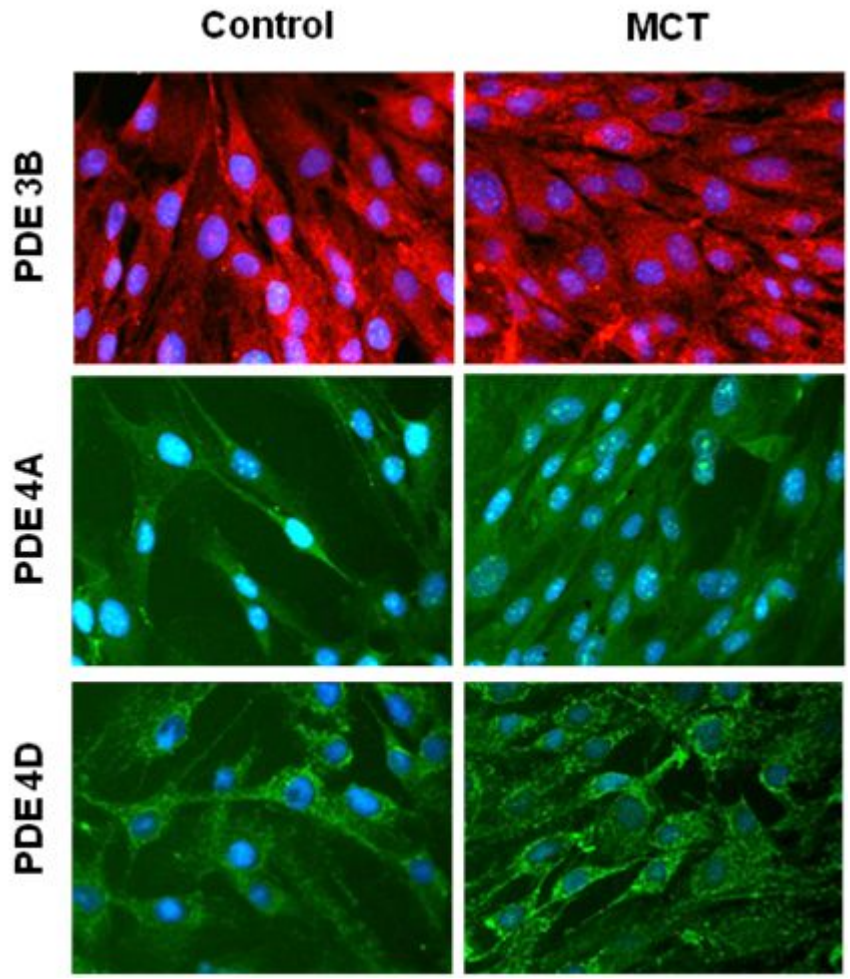

Figure 7: PDE 3 and 4 expression in monocrotaline-induced PAH

The research areas were supported by the European PH registry, biobank, clinical trial unit, proteomics and gene array platforms, specialist SME (yeast-two-hybrid, siRNA, oxygen sensing agents and techniques, technology transfer).

Several partners of the PULMOTENSION consortium engaged in the clinical care of PAH patients were involved in the World Symposium on PAH (Dana Point 2008), where new classification and guidelines were discussed and updated (JACC 54: S43-54, 2009) and several partners are members of the Task Force "Diagnosis and Treatment of PH" of the European Cardiology Society and the European Respiratory Society, recently having published guidelines for diagnosis and treatment of PH (Eur Respir J: 34: 1219-1263).

2. Dissemination and use

Title	Date (accept / release)	Authors	Publication	WP	Lead contractor
Cross-talk between endothelial and smooth muscle cells in pulmonary hypertension: serotonin-induced smooth muscle hyperplasia	2006	Eddahibi S, …Dewachter L, …Humbert M, Simonneau G, …Adnot S	Circulation 113: 1857-1864	E3	INSERM
Interleukin-6 Gene Polymorphism confers susceptibility to pulmonary hypertension in chronic obstructive pulmonary disease	Aug 2006	S Eddahibi, S Adnot	Proc Am Thorac Soc 3: 475-476	E3	INSERM
Transgenic Mice Overexpressing the 5-Hydro-xytryptamine Transporter Gene in Smooth Muscle Develop Pulmonary Hypertension	Sept 2006	Serge Adnot	Circulation Research	E3	INSERM
Dendritic cell recruitment in lesions of human and experimental pulmonary hypertension	Oct 2006	Marc Humbert	European Respiratory Journal	B1	HOAB
Angiopoietin/Tie 2 pathway influences smooth muscle hyperplasia in idiopathic pulmonary hypertension	Nov 2006	Dewachter L, Adnot S, … Humbert M,… Simonneau G, …Naeije R, Eddahibi S	Am J Respir Crit Care Med 174: 1025-1033	E3	INSERM/ ULB/HOAB
Fractalkine-induced smooth muscle cell proliferation in pulmonary hypertension	E pub Dec 2006, in print 2007	F Perros, …, S Adnot, S Eddahibi, …, M Humbert	Eur Resp 29: 937-942	B1 / E3	HOAB / INSERM
Dysregulated bone morphogenetic protein signaling in monocrotaline-induced pulmonary arterial hypertension	Feb 2007	RE Morty, …, W Seeger, RT Schermuly, O Eickelberg	Arterioscler Thromb Vasc Biol 27: 1072-1078	E2	UGLC-c, UGLC-a
Disruption of methylarginine metabolism impairs vascular homeostasis	Feb 2007	J Leiper, …, P Vallance	Nat Med 13: 198-203	F2	UCL
Phosphodiesterase 1 upregulation in pulmonary arterial hypertension	Feb 2007	RT Schermuly, N Weissmann, HA Ghofrani, C Schudt, …, W Seeger, F Grimminger	Circulation 115: 2331-2339	F4 / G1	UGLC-b / UGLC-d / UGLC-a / Altana (=Nycomed)
Optical analysis of the HIF-1 complex in living cells by FRET and FRAP	Mar 2007	C Wotzlaw, …, J Fandrey	FASEB J 21: 700-707	A1	UDE

Receptor for activated C-kinase 1, a novel interaction partner of type II bone morphogenetic protein receptor, regulates smooth muscle cell proliferation in pulmonary arterial hypertension	Mar 2007	A Zakrzewicz, …, W Seeger, …, RT Schermuly, NW Morrell, RE Morty, O Eickelberg	Circulation 115: 2957-2968	E2	UGLC-c / UGLC-a / UCSM
The ADMA pathway is a critical regulator of endothelial cell motility	Mar 2007	…, Leiper JM, Vallance P.	J Cell Sci. 2007 Mar 15;120	F2	UCL
Enhanced susceptibility to suicidal death of erythrocytes from transgenic mice overexpressing erythropoietin	May 2007	Föller M, …, M Gassmann, F Lang	Am J Physiol Regulatory Integrative Comp Physiol: 1127-1134	A4	UZ
Acute and chronic exposure to hypoxia alters ventilatory pattern but not minute ventilation of mice over-expressing erythropoietin	May 2007	J Soliz, …, M Gassmann	Am J Physiol Regulatory Integrative Comp Physiol: 1702-1710	A4	UZ
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Cellular origin of pro-coagulant and (anti-)-fibrinolytic factors in bleomycin-injured lungs	June 2007	M Wygrecka, …, KT Preissner, W Seeger, A Guenther	Eur Respir J 29: 1105-1114	B2	UGLC
BMP4 induces HO-1 via a smad-independent p38 MAPK-dependent pathway in pulmonary artery myocytes	June 2007	X Yang,…, RC Trembath, NW Morrell	Am J Respir Cell Mol Biol 37: 598-605	E1	UCSM / KCL
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Imaging of the heart in pulmonary hypertension	Sept 2007	L. McLure/A. Peacock	Int J Clin Pract (suppl) 156: 15-26	G3	SPVU
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Partial reversal of experimental pulmonary hypertension by phospho-diesterase 3,4 inhibition	Nov 2007 (epub)	E Dony, …, HA Ghofrani, N. Weissmann, C Schudt, W Seeger, F Grimminger, RT Schermuly	Eur Respir J 31: 59-610	F4 / G1	UGLC-b / UGLC-d / UGLC-a / Altana (=Nycomed)
Asymmetric dimethylarginine is increased in CTEPH	Dec 2007	Skoro-Sajer N,…, Lang IM	Arterioscl Thromb Vasc Biol 28	B2	MUV
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Platelet-derived growth factor expression and function in idiopathic pulmonary arterial hypertension.	July 2008	…, Simonneau G, …, Humbert M	American Journal of Respiratory and Critical Care Medicine	B1	HOAB
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Abnormal sympatho-adrenal development and systemic hypotension in PHD3-/-mice	Mar 2008	Bishop T, …Pugh CW, Ratcliffe PJ	Mol Cell Biol 28, 3386-3400	A3	UOXF
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Mutation of the von Hippel-Lindau gene alters human cardiopulmonary physiology	2008	Smith TG, …, Pugh CW, …	Adv Exp Med Biol 605:51-6	A3	UOXF
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Activin-A, transforming growth factor-beta, and myostatin signalling pathway in experimental dilated cardiomyopathy	Oct 2008	Mmahmoudabad y M, …, Dewachter L, …, Naeije R, …	J Card Fail	C2	ULB
The emerging role of magnetic resonance imaging in the diagnosis and management of pulmonary hypertension	Nov 2008	Kovacs G, …, Peacock A, Olschewski H	Respiration 76:458-470	G3	SPVU/MUB
Inhibition of PDE4 enhances lung alveolarisation in neonatal mice exposed to hyperoxia	Nov 2008, epub	…, Weissmann N, Ghofrani HA, Seeger W, Grimminger F, Morty RE, Schermuly RT	Eur Respir J 33: 861-870	G1	UGLC
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First acute haemodynamic study of soluble guanylate cyclase stimulator riociguat in pulmonary hypertension	Jan 2009	Grimminger F, … Voswinckel R, …, Weissman N, … Schermuly RT, Ghofrani HA	Eur Respir J 33: 785-792	F4	UGLC
Endothelin-1 inhibits background Two-pore-domain cahnnel TASK-1 in primary human pulmonary artery smooth muscle cells	Feb 2009, epub	Tang B, … Voswinckel R, Weissmann N, …Olschewski H, Olschewski A	Am J Respir Cell Mol Biol	B2	MUG/UGLC
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Evidence of dysfunction of endothelial progenitors in PAH	July 2009	Toshner M, Voswinckel R,…Seeger W, Pepke-Zaba J, Morrell NW	Am J Respir Crit Care Med 180: 780-787	D2/ D1	UCSM/ UGLC
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Erythropoietin activates nitric oxide synthase in murine erythrocytes	Aug 2009	…Vogel J, Gassmann M, Bogdanova A	Am J Physiol 297: C378-388	A4	UZ
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Sequence variants in BMPR2 and genes involved in the serotonin and NO pathways in IPAH and CTEPH: Relation to clinical parameters and comparison with left heart disease	Oct 2009, epub	… Szamalek-Hoegel J, …Gruenig E, Janssen B, …	Respiration 79: 279-287	F1	UKL-HD
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Hemodynamic and gas exchange effects of sildenafil in patients with COPD and PH	Dec 2009	Blanco I, …Rodriguez-Roisin R, Roca J, Barbera JA	Am J Respir Crit Care Med 181: 270-278	D3	HCPB
Pulmonary vascular remodelling correlates with lung eggs and cytokines in murine schistosomiasis	Dec 2009	… Schermuly R, Butrous G, … Morrell NW	Am J Respir Crit Care Med 181: 279-288	E1	UCSM
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