Deutsches Zentrum für Lungenforschung

DZG DEUTSCHE ZENTREN DER GESUNDHEITSFORSCHUNG

German Center for Lung Research

Annual Report 2012

Translational Research to Combat Widespread Lung Diseases

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Forward

Lung diseases rank amongst the deadliest killers, not only in Germany, but worldwide. In spite of the enormous public health problem, the range of therapies available to patients with lung disease is relatively low compared to other diseases. At the Germen Center for Lung Research (Deutsches Zentrum für Lungenforschung, DZL) we want to change this reality. By bringing together leading scientists and clinicians in the field of pulmonary research and providing them with common tools, infrastructure, and resources we create the ideal conditions for the rapid development of innovative new therapies for patients with lung disease.

The close integration of basic, translational, and clinical scientists all engaged in pulmonary research means that new findings in the laboratory can be rapidly translated into clinical practice. At the DZL we aim not only to change the speed of medical innovation, but to bring to the pulmonary field an entirely new dimension of preventative, diagnostic, and treatment options for patients with lung disease. Through the innovation of DZL scientists and clinicians, therapies for lung disease may look completely different tomorrow than they do today. We invite you here to learn more about our progress combatting some of the world's deadliest diseases.

Professor Dr. Werner Seeger
Chairman and Speaker of the DZL

About the DZL

Lung diseases rank second with respect to morbidity and mortality worldwide. The World Health Organization lists four lung diseases among the top ten causes of death on a global level, and every fifth death is caused by lung disease or the consequences thereof. The European Respiratory Society estimates the direct and indirect costs of lung disease are more than 100 billion € per year for Western Europe alone. For most respiratory diseases currently available treatment concepts provide symptomatic relief but no cure. Moreover, the incidence and economic burden of lung disease are expected to grow even further over the next decades. For these reasons, it is more important than ever to develop new approaches to combatting lung disease, including options for disease prevention, diagnosis, and therapy.

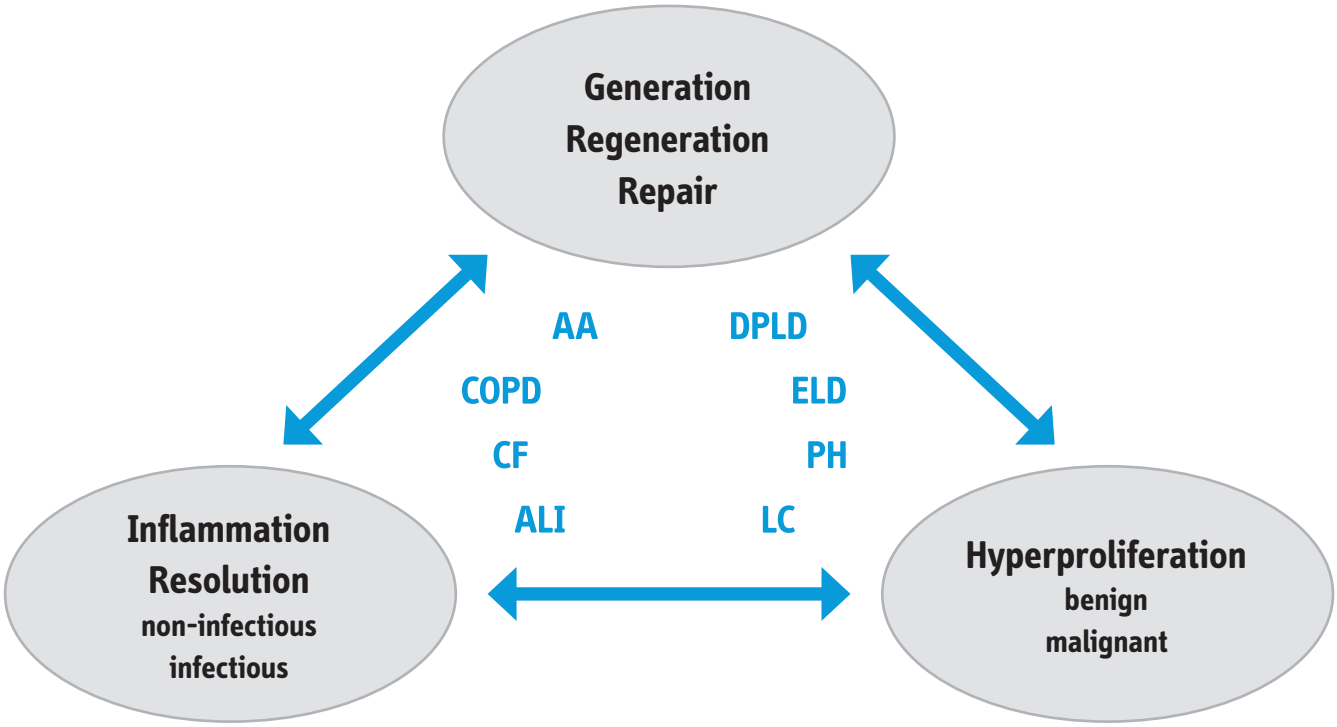
The German Center for Lung Research (DZL) is an association of the leading university and non-university institutions dedicated to lung research in Germany. With the mission of using “translational research to combat widespread lung diseases,” the DZL seeks to jointly develop new approaches for the prevention, diagnosis and therapy of severe lung diseases including asthma, chronic obstructive pulmonary disease (COPD) , cystic fibrosis, diffuse parenchymal lung disease (DPLD), end-stage lung disease, lung cancer, pneumonia and acute lung injury, and pulmonary hypertension.

Science – Translation in Focus

Translational research is the process of transforming scientific discoveries arising from the laboratory into practical applications that directly impact human health and well-being. For each of the diseases studied by DZL scientists, the entire "bench-to-bedside" translational research chain runs the gamut from investigation of molecular signatures and pathways of disease in animal and laboratory models to the use of those data to drive the design and implementation of clinical trials and patient care. This process is achieved by the close integration of basic scientists and clinicians and is facilitated by regular meetings, symposia, and access to common infrastructure.

Lung diseases are multi-dimensional, affecting the airways, lung tissue, and pulmonary vasculature. Nevertheless, there is substantial mechanistic overlap as to disease initiation and progression among all disease areas studied by the DZL. The integrated scientific approach being put into practice explores the dynamic relations among 1) lung generation, regeneration, repair; 2) inflammation and its resolution; and 3) hyperproliferation and its control across all DZL disease areas. Findings in one disease area may thus be applicable across several disease areas, and the DZL scientific approach and infrastructure allow for rapid translation of findings across diseases.

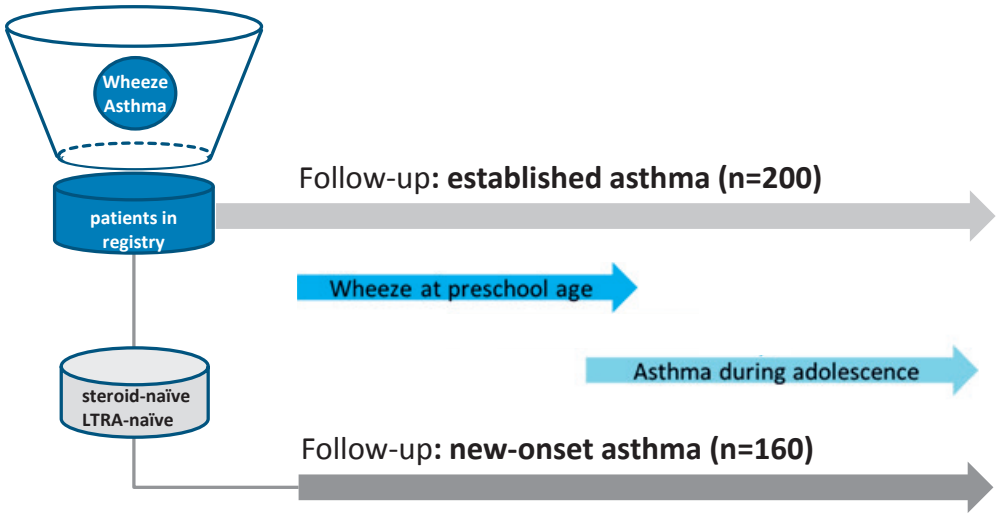
In order to achieve its scientific and clinical goals, the DZL is organized around the concept of Disease Areas. Each Disease Area team consists of clinicians and basic scientists working together to advance treatments and therapies for a specific indication. Working in concert with the DZL Executive Board, elected Disease Area leaders set goals and milestones for each Disease Area and monitor progress. Each Disease Area team is supported by a coordinator, and progress is reported to the DZL Executive board no less than every six months. Not working in isolation, each Disease Area team has access to common infrastructure and resources. Furthermore, many investigators belong to more than one Disease Area team, allowing for cross-fertilization of ideas and findings across research areas.



Asthma and Allergy

Disease Area Leaders	Prof. Dr. Heinz. Fehrenbach (ARCN) Prof. Dr. Erika von Mutius (CPC-M)
Participating DZL Partner Sites	ARCN, BREATH, UGMLC, TLRC, CPC-M
Number of Participating DZL Faculty	40

Asthma is the most prevalent chronic respiratory disease in childhood and is also very common in adults. Although the clinical manifestations of asthma in children and adults is rather uniform with wheezing, shortness of breath and cough, population-based clinical and genetic studies suggest that asthma is not one disease, but many. Thus, a single "one-size-fits-all" treatment approach is unlikely to work to tackle this important health problem. In order to design personalized treatment approaches for asthma patients, there is urgent need to elucidate the mechanisms underlying the various types of asthma. The decoding of such mechanisms and their translation to the individual patient is the aim of the Asthma and Allergy team of the DZL.



In order to decode mechanisms that may underlie development of distinct wheeze and asthma phenotypes in childhood, the Disease Area follows two approaches. (1) A database will be created as a clinical registry, which includes all clinical data of all patients with wheeze and asthma seen in asthma clinics in the three centers ARCN, BREATH, CPC-M (N=3,000 children). (2) In order to perform deep phenotyping (detailed characterization) with the goal of identifying possible biomarkers for these distinct wheeze and asthma phenotypes in childhood in addition to collecting the same clinical data as in children from the registry, a clinical cohort will be created. This cohort will allow deep phenotyping of young wheezy children and asthmatic adolescents, respectively, (a) for children with established diagnoses ("established asthma", n=200 out of N=3,000, upper part) and (b) for children with new-onset disease, which are – due to their early disease stage – still naïve with regard to the use of medications that may impact immune responses, i.e. steroids and leukotriene receptor antagonists (n=160, lower part). Children in the register and cohort will be followed up yearly in addition to clinical routine visits until at least 2015 and beyond.

Goals Followed in 2012 – Asthma and Allergy

Goal 1 – German Collaborative Asthma Cohort

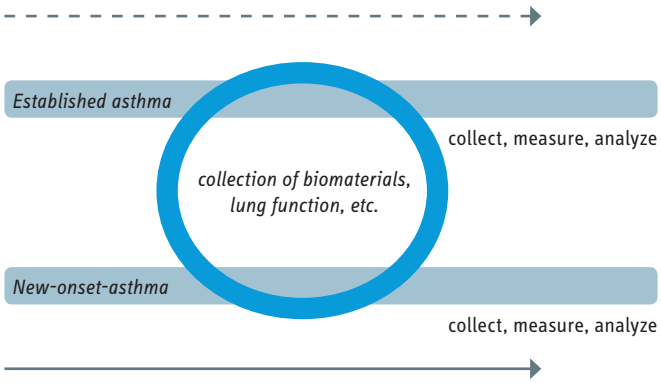
- Building an asthma and allergy patient registry
- Integrating clinical and "omics" data by means of systems biology approaches

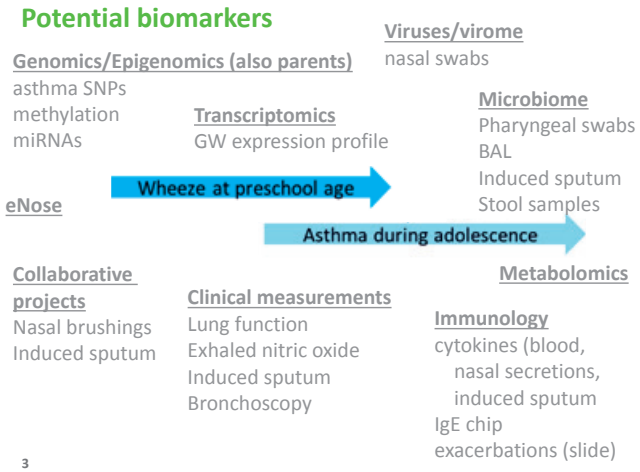
Goal 2 – Mechanisms Underlying the Development of Asthma Phenotypes

- Translational models of asthma phenotypes
  - Establishment of novel phenotype-specific murine models (incl. transgenic models) for mechanistic (e.g. pathogenetic role of granulocytes, T and B cells) and pre-clinical studies
  - Generation of Drosophila models for the functional characterization of novel candidate genes for asthma
- Cellular mechanisms
  - Identification of structural and functional properties of allergens that can lead to qualitatively different immune responses (dimer/oligomer formation; epitope mapping)
  - Characterization of the role of the airway epithelium in the formation of distinct asthma phenotypes (epithelial signatures)
  - Identification of individual genes and pathways in tissues of the epithelial-mesenchymal trophic unit and nervous system with key features in the pathogenesis of asthma (remodeling, bronchoconstriction)
  - Analysis of the importance of the innate immune system in the pathogenesis of distinct asthma phenotypes
  - Identification of phenotype-specific components of the adaptive immune system (imprinted phenotypes, cell differentiation, role of specific cell subtypes, chipcytometry)
  - Identification of new biomarkers and molecular targets for asthma phenotypes
  - Establishment and application of a lipidomics platform
- Genetic, epigenetic, and microbiome analyses
  - Analysis of epigenetic signatures (in particular chromatin modifications) in human BAL and blood samples from an asthma cohort
  - Establishment and use of systems biology platform

2012 Research Highlights – Asthma and Allergy

Research Highlight #1





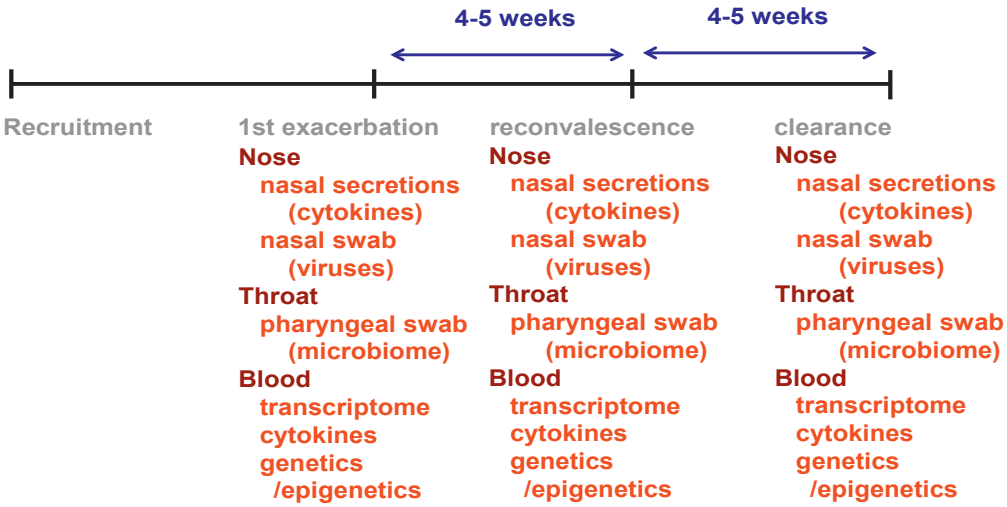
For both children with established diagnoses and new-onset disease, the collection of biomaterial and of clinical data and clinical measurements such as lung function and markers of allergic airway disease will start in early 2013 (blue circle). These data may aid the identification of biomarkers for distinct wheeze and asthma phenotypes in childhood that can be discovered in children with established diagnosis of wheeze or asthma in the clinical setting (upper dashed arrow) and replicated in children with new-onset disease, for whom disease course can be followed more precisely but who will more often be seen in a primary care setting (vs. clinical setting) due to their premature disease state (lower solid arrow).

Using a systems biology approach integrating clinical and "omics" data from several body compartments, potential biomarkers will be analyzed for their use in differentiating distinct wheeze and asthma phenotypes in childhood. During 2012, all these platforms have been built up (many of them in collaborative projects) and collection of biomarkers will start in 2013.

(BAL - bronchoalveolar lavage; eNose – electronic nose; GW – genome wide; IgE – immunoglobulin E; miRNA - microRNA; SNP – single-nucleotide polymorphism)

Epithelial cells isolated from nasal (adults, children) and bronchial (adults only) brushings, in addition to epithelial secretions and inflammatory cells obtained from swabs, sputum and/or broncho alveolar lavage (BAL), are the few biomaterials that can be collected directly from the organ of interest, i.e. the lungs and airways. Therefore, a major focus of goal 2, the investigation of cellular mechanisms underlying specific asthma phenotypes, is the elucidation of epithelial cell signatures and nasal/bronchial secretions as important sources of potential phenotype-specific markers. In 2012 through 2013, principal investigators at two centers, ARCN and CPC-M, are establishing SOPs for the collection, processing, transfer, storage, and analysis of sputum, swabs and epithelial brushings. In addition, a collaborative pilot project was initiated across the two centers to assess the suitability of primary epithelial cells obtained from brushings of the nose and bronchi in adults for proof-of-principle experiments performed in vitro. Consequently, the role of the airway epithelium in the pathogenesis of asthma phenotypes is a major research focus within this Disease Area.

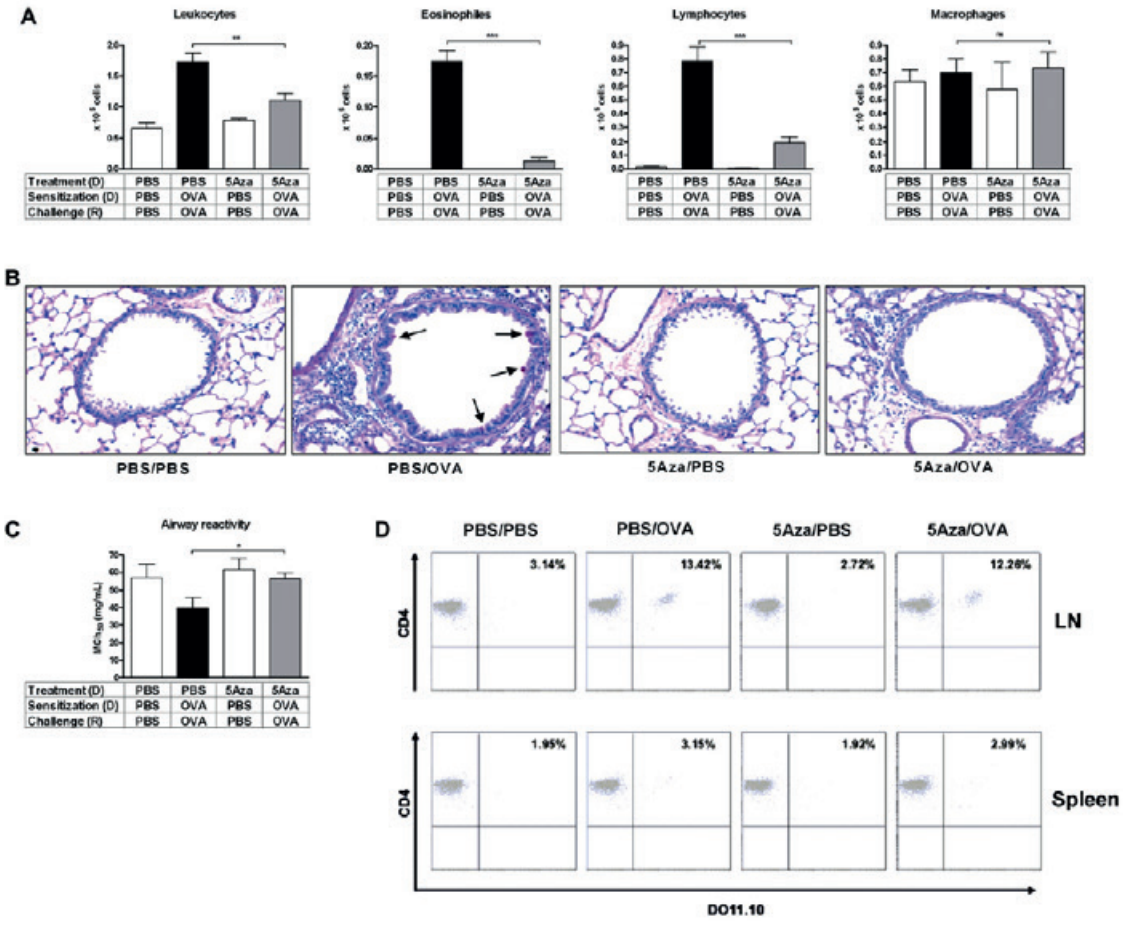
Research Highlight #2



Within the group of young wheezy children (age 6 months up to 6 years) a specific hypothesis will be tested underlining the prospective approach in children with medication-naïve new-onset disease. We hypothesize that children with persistent wheeze and increased risk for later asthma differ from children with transient wheeze in their immune response and exhibit delayed viral clearance as well as a distinct microbiome in their upper airways. In a collaborative effort, the Disease Area will analyze whether there are such differences between children with future asthma whose symptoms are usually triggered by infections and additional triggers such as exercise or allergens, and those children whose symptoms are merely triggered by infections and grossly outgrow their disease. Here, analyses will include that of the virome (collective genomes of viruses in the nasopharyngeal space), the microbiome (collective genomes of bacteria in the upper airways) and the children's immune responses to viruses and bacteria in the context of their genetic background. After initial recruitment and collection of biomaterial, further biomaterial will be sampled after the first clinical exacerbation and at 4-5 and 8-10 weeks post.

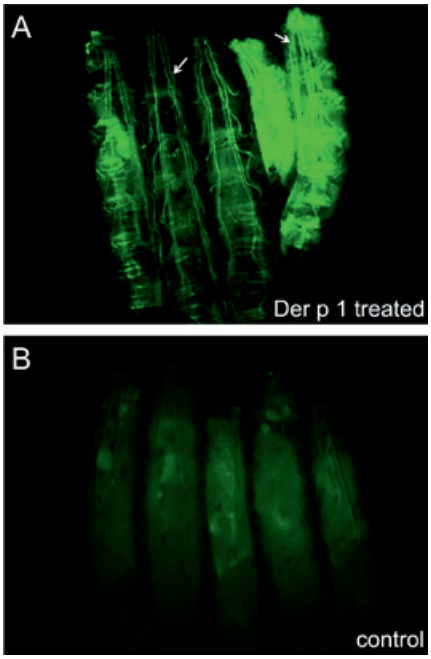
Research Highlight #3

Genetic, epigenetic, and microbiome analyses: Analysis of epigenetic signatures. Here, CD4+ T cells were shown to exhibit a significant increase in DNA methylation at the IFNG promoter after allergen sensitization/challenge, which could be reversed with a DNA methyltransferase (DNMT) inhibitor in vitro and in vivo including adoptive transfer experiments with CD4+ T cells from DNMT treated donor mice.



*Treatment with 5Aza blocks development of an asthmatic phenotype by adoptively transferred CD4+ T cells from DO11.10 donor mice. A-C, Differential leukocyte numbers in BAL fluid (A), inflammation and mucus-producing goblet cells (arrows) in the airways (B), and airway responsiveness to methacholine in recipients (C). D, Percentage of DO11.10+ cells within CD4+ T cells in lymph nodes and spleens of recipient mice. Given are means ± SEMs from 4 to 6 individually analyzed animals per group. **P < .05, **P < .01, and ***P < .001. ns, Not significant.*

(Reprinted from] Allergy Clin Immunol, 129(6), Brand, et al, DNA methylation of TH1/TH2 cytokine genes affects sensitization and progress of experimental asthma. Pages 1602-1610. Copyright 2012, with permission from Elsevier.)



Research Highlight #4

In Research Highlight #4, it was demonstrated that Dermatophagoides pteronyssinus major allergen 1 (Der p 1), the major allergen of the house dust mite, efficiently activates various facets of the Drosophila innate-immune system, including both epithelial and systemic responses. These responses depend on the immune deficiency (IMD) pathway via activation of the NF-κB transcription factor Relish.

Der p 1 induced an epithelial immune response in the airways. (A) Incubation of Drosophila larvae carrying a drosomycinP-gfp construct with Der p 1 (100 nM) induced expression of the reporter in the trachea only (arrow). (B) Control larvae of the same genotype and age were treated exactly as those above, but Der p 1 was omitted. Median larval length is ~2 mm.

(Fig. from: Warmbold C et al. Dermatophagoides pteronyssinus major allergen 1 activates the innate immune response of the fruit fly Drosophila melanogaster. J Immunol. 2013; 190: 366-71. Copyright 2013. The American Association of Immunologists, Inc.)

Number of papers published by DZL Faculty in 2012 – Disease Area Asthma and Allergy: 38

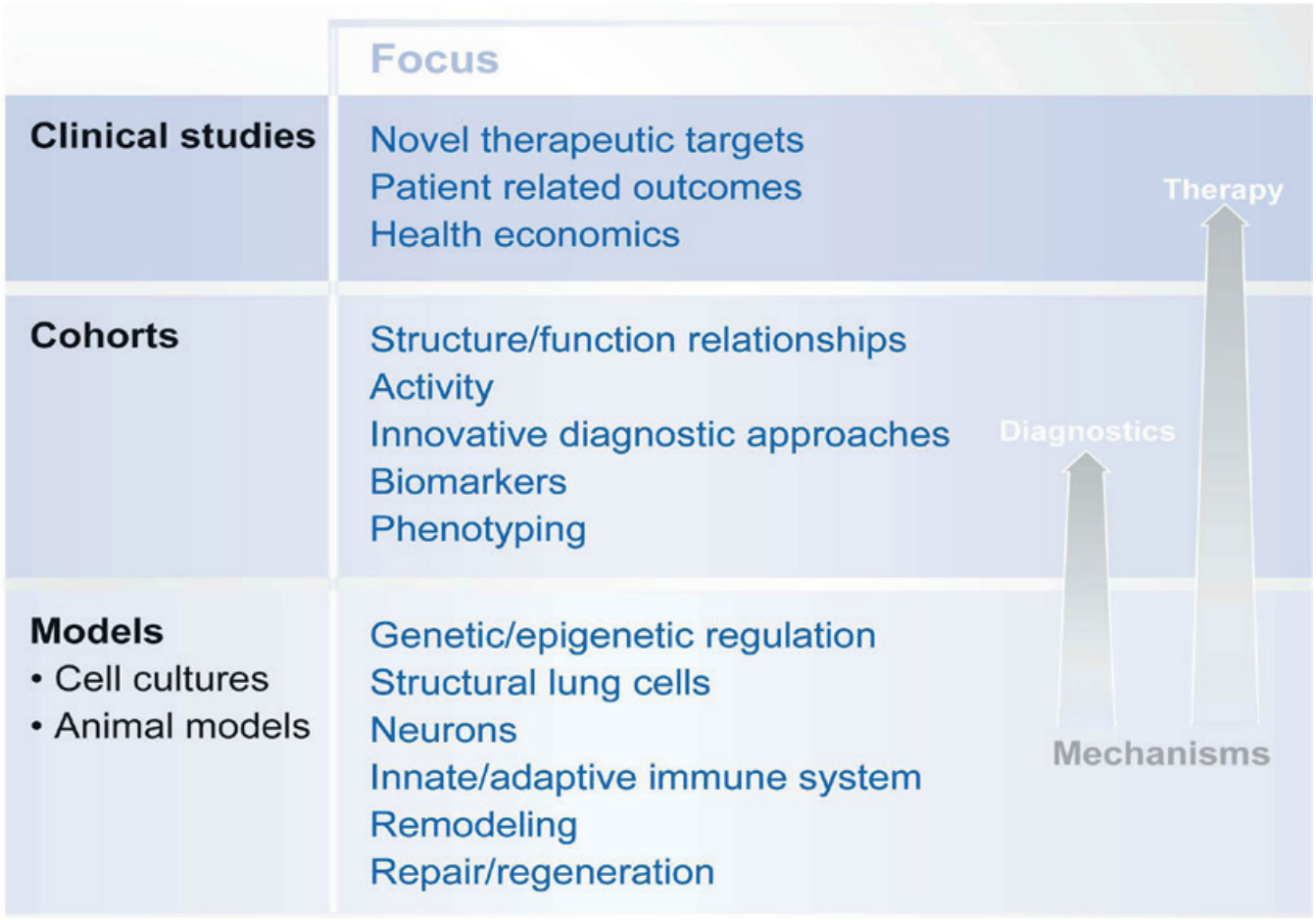
Highlighted Publications

1. Klaenhammer TR, Kleerebezem M, Kopp MV, Rescigno M. The impact of probiotics and prebiotics on the immune system. Nat Rev Immunol 2012; 12: 728-34.
2. Anagnostopoulou P, Riederer B, Duerr J, Michel S, Binia A, Agrawal R, Liu X, Kalitzki K, Xiao F, Chen M, Schatterny J, Hartmann D, Thum T, Kabesch M, Soleimani M, Seidler U, Mall MA. SLC26A9-mediated chloride secretion prevents mucus obstruction in airway inflammation. J Clin Invest 2012; 122: 3629-34.
3. Warmbold C, Uliczka K, Rus F, Suck R, Petersen A, Silverman N, Ulmer AJ, Heine H, Roeder T. Dermatophagoides pteronyssinus major allergen 1 activates the innate immune response of the fruit fly Drosophila melanogaster. J Immunol 2013; 190: 366-71.
4. Busse M, Krech M, Meyer-Bahlburg A, Hennig C, Hansen G. ICOS mediates the generation and function of CD4+, CD25 l+, Foxp3+ regulatory T cells conveying respiratory tolerance. J Immunol 2012; 189: 1975-82.
5. Brand S, Kesper DA, Teich R, Kilic-Niebergall E, Pinkenburg O, Bothur E, Lohoff M, Garn H, Pfefferle PI, Renz H. DNA methylation of TH1/TH2 cytokine genes affects sensitization and progress of experimental asthma. J Allergy Clin Immunol 2012; 129: 1602-10.

Chronic Obstructive Pulmonary Disease (COPD)

Disease Area Leaders	Prof. Dr. Klaus F. Rabe (ARCN) Prof. Dr. Claus F. Vogelmeier (UGMLC)
Participating DZL Partner Sites	ARCN, BREATH, UGMLC, TLRC, CPC-M
Number of Participating DZL Faculty	49

Chronic Obstructive Pulmonary Disease (COPD) is characterized by progressive and largely irreversible airflow limitation. Shortness of breath is the most common symptom of COPD and contributes significantly to the decreased quality of life experienced by many COPD patients. Although in part preventable, COPD is the 4th leading cause of death in the world. The most common causes of COPD are cigarette smoking and air pollution, and the most frequently encountered destructive lung disease is COPD linked to emphysema. Loss of structural integrity and regenerative capacity are critical for disease progression as well as for response to or lack of response to therapy in COPD; however the underlying mechanisms remain poorly understood. The long term goal of the DZL COPD research effort is the translation of novel mechanism-based therapeutic concepts into effective therapies for COPD patients.



Goals Followed in 2012 – COPD

Goal 1 – Remodeling, Regeneration and Repair: From Animal Models to Human Tissues

- Development of conditional mouse models for chronic bronchitis and emphysema by regulated overexpression of ENaC in Clara cells and alveolar type II cells
- Validation of candidate genes in native tissues and primary cultures of COPD
- Transcriptome analysis and target validation in human samples (sputum, lung tissue)

Goal 2 – Biomarkers and Phenotypes

- Biomarkers in exhaled breath and the airway surface liquid
  - Development, improvement and standardization of sampling techniques for volatile molecules (VOC)
  - Standardized collection of VOCs in COPD patients
  - VOC analysis of COPD cohorts
  - Identification and development of biomarkers in epithelial fluid by means of bronchoscopic microcollection and exhaled particle analysis
- Imaging Biomarkers
  - Development and adaptation of MRI sequences for the detection, quantification and monitoring of inflammatory airway changes
  - Determination of airway inflammation and local ventilation by MRI in healthy subjects after segmental endotoxin challenge
  - Determination of airway inflammation in COPD patients by MRI
  - MRI imaging in patients with COPD severity GOLD A - D
- FRET-based sensors for quantitative monitoring of pulmonary inflammation and proteolysis
  - Development of sensitive and specific FRET sensors to determine the activity of pulmonary proteases (MMP12, neutrophil elastase, cathepsins)
- Mucins
  - Development of mucin-reactive probes

Goal 3 – Measurement of Physical Activity

- Establishment of protocols and testing at sites

Goal 4 – Cohorts and Clinical Studies

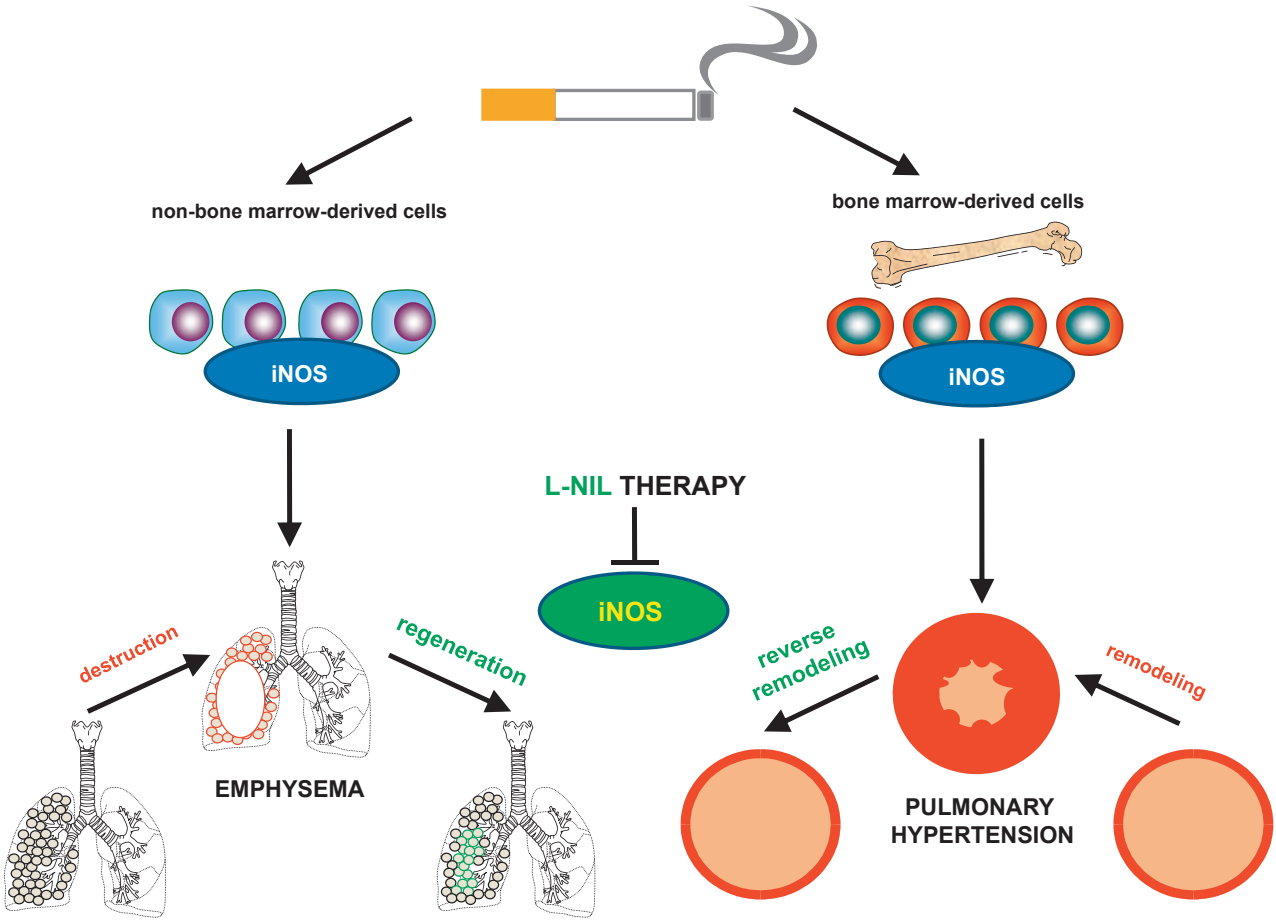
- Implementation of cohort studies
- Clinical trials in cooperation with industry partners
- Implementation of Investigator Initiated Trials following approval by the DZL “Clinical Trials Board”

Goal 5 – Healthcare Management and Healthcare Economics

- Listing of complete data requirements; systematic literature review of project-specific survey instruments
- Obtain approval for data protection concept and approval of the Ethics Committee
- Software selection and completion of programming and interface adaptation

2012 Research Highlights – COPD

Research Highlight #1:

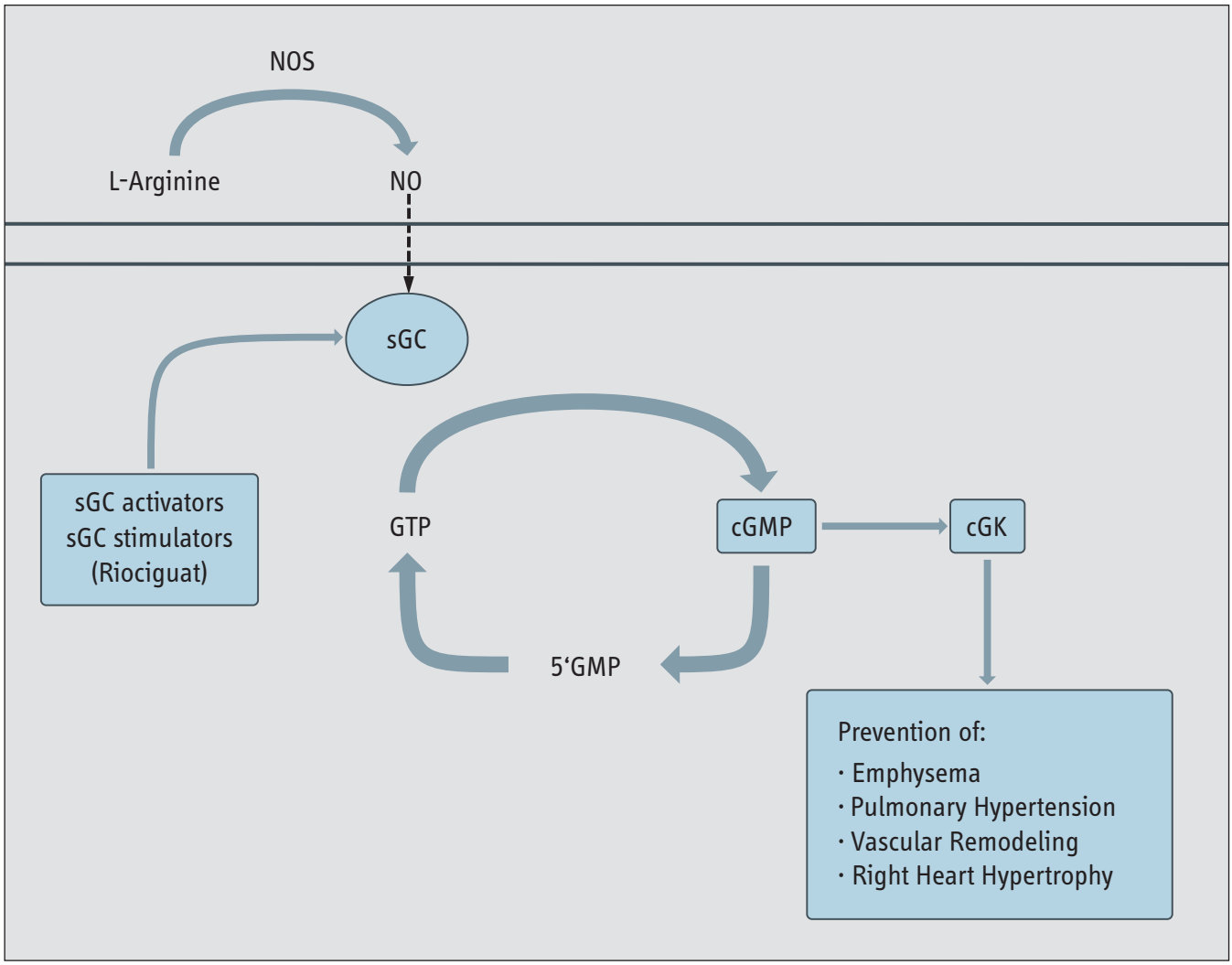


We showed in a mouse model of chronic tobacco smoke exposure that pulmonary vascular dysfunction, vascular remodeling, and pulmonary hypertension (PH) preceded development of alveolar destruction. As a causative factor an upregulation of the inducible nitric oxide synthase (iNOS) and peroxynitrite was suggested. Both genetic iNOS deletion as well as pharmacological inhibition of iNOS prevented emphysema and PH development. In a curative treatment approach the iNOS inhibitor N6-(1-iminoethyl)-L-lysine (L-NIL) reversed established disease.

By investigation of chimeric mice we found that PH was dependent on iNOS from Bone Marrow (BM)-derived cells, whereas emphysema development was dependent on iNOS from non-BM-derived cells. A comparison with lung tissue from end-stage COPD patients revealed similar regulatory and structural alterations as in mouse lungs.

(Reprinted from Cell, 147(2), Seimetz et al., Inducible NOS Inhibition Reverses Tobacco-Smoke-Induced Emphysema and Pulmonary Hypertension in Mice. Pages 293-305. Copyright 2011, with permission from Elsevier.)

Research Highlight #2:

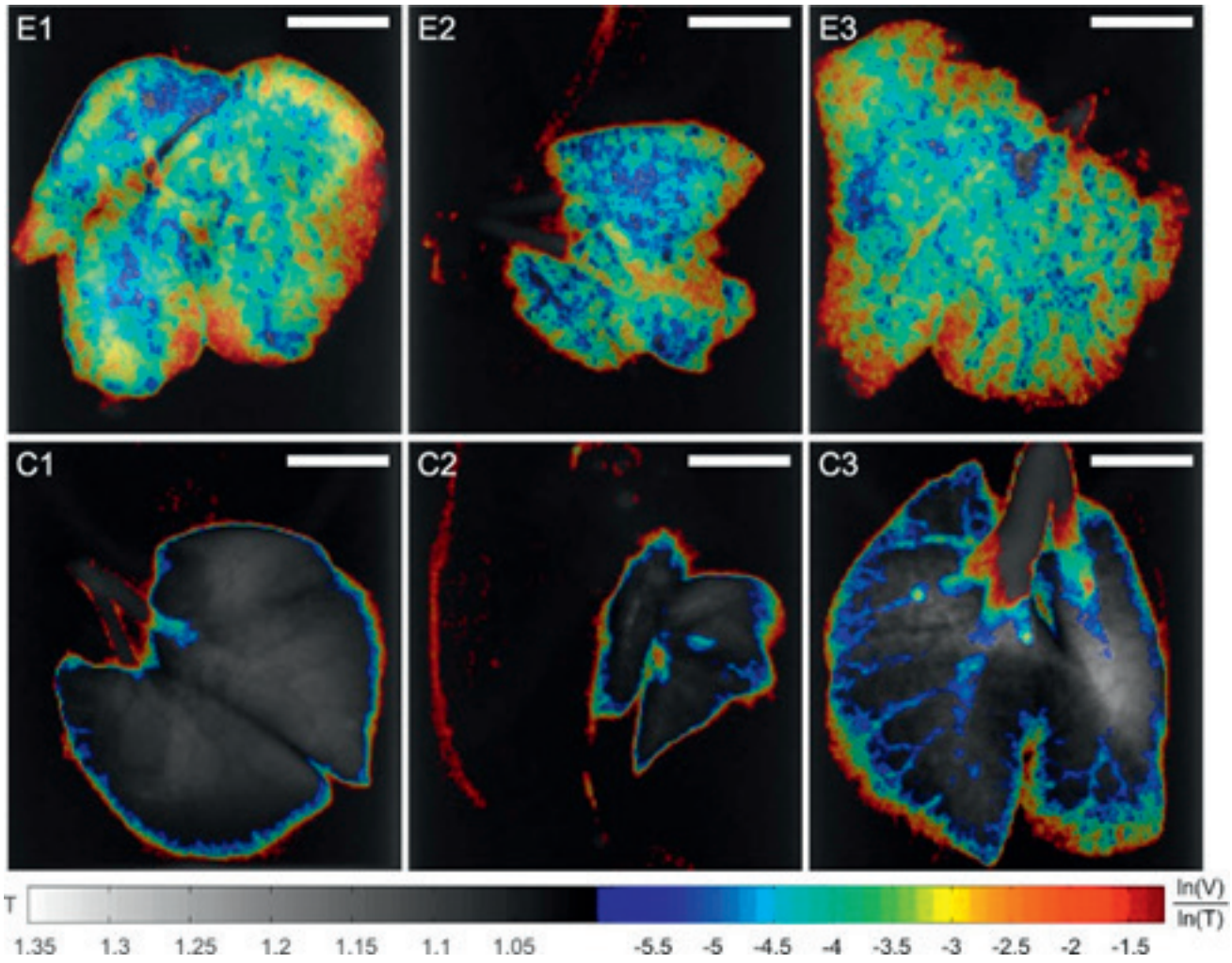


Preventative Riociguat Treatment in a Smoke Model

We hypothesized that soluble guanylate cyclase is a possible downstream target of ONOO- and thus, in a preventive approach, treated mice with the soluble guanylate cyclase stiumulator riociguat in parallel with smoke exposure. Riociguat prevented the development of pulmonary hypertension as well as emphysema, leading to the hypothesis that down-regulation of essential guanylate cyclase subunits may be an underlying mechanism contributing to the development of these conditions.

(NO – nitric oxide; NOS – nitric oxide synthase; sGC – soluble guanylate cyclase)

Research Highlight #3:



In early stages of emphysema, the change in X-ray attenuation is not detectable with absorption-based radiography. To monitor the morphological changes that the alveoli network undergoes in the progression of these diseases, we propose using the dark-field signal, which is related to small-angle scattering in the sample. Combined with the absorption-based image, the dark-field signal enables better discrimination between healthy and emphysematous lung tissue in a mouse model.

The figure shows multimodal projections of three emphysematous lung samples (E1, E2, E3) and three control lung samples (C1, C2, C3). To visualize the apparent differentiation of healthy and emphysematous lungs from the scatter plot, we propose using threshold values on the quotient of the logarithm of dark-field contrast and transmission values ln(V)/ln(T) = -6 and ln(V)/ln(T) = -1.2. In single projections, the corresponding pixels have been superimposed on the conventional transmission contrast image

with their color representing ln(V)/ln(T). Standard transmission is depicted in the linear gray scale with transmission values (with respect to water) ranging from 1 to 1.35. The material-dependent quotient ln(V)/ln(T) is displayed in jet colors ranging from -6 to -1.2, where higher values (yellow, red) correspond to lower scattering at similar transmission and thus larger mean alveoli diameter (Scale bars: 5mm; PNAS 2012; 109:17880-5, © National Academy of Sciences).

Research Highlight #4:

Cohorts and Clinical Trials COSYCONET

COPD – Systemic Consequences & Comorbidities

Primary aim

- Extrapulmonary organ manifestations / disorders → risk for progression of COPD

Secondary aims

→ patterns of extrapulmonary disorders (functional, clinical, systemic)
→ morbidity, mortality, prognosis, comparison with population data
→ development / time course of extrapulmonary disorders
→ novel phenotypes of COPD
→ impact of systemic inflammation, clinical value of blood markers
→ role of age / premature ageing
→ health care utilization due to comorbidities

COSYCONET is a large longitudinal cohort of patients with COPD with a clear focus on comorbidities. Cardiovascular comorbidities, which account for approximately one-third of deaths of all patients with COPD irrespective of disease severity, are objectively assessed by measurement of ankle-brachial index and echocardiography, performed according to current standards in cardiology. The DZL partners in this cohort project have already recruited approximately 1000 patients, nearly half of the study population. The patients in this cohort are very well characterized and form a solid basis for research questions on COPD in the DZL ranging from basic science, biomaterials, and therapeutic interventions, to care models of chronic disease.

Number of papers published by DZL Faculty in 2012 - Disease Area COPD: 54

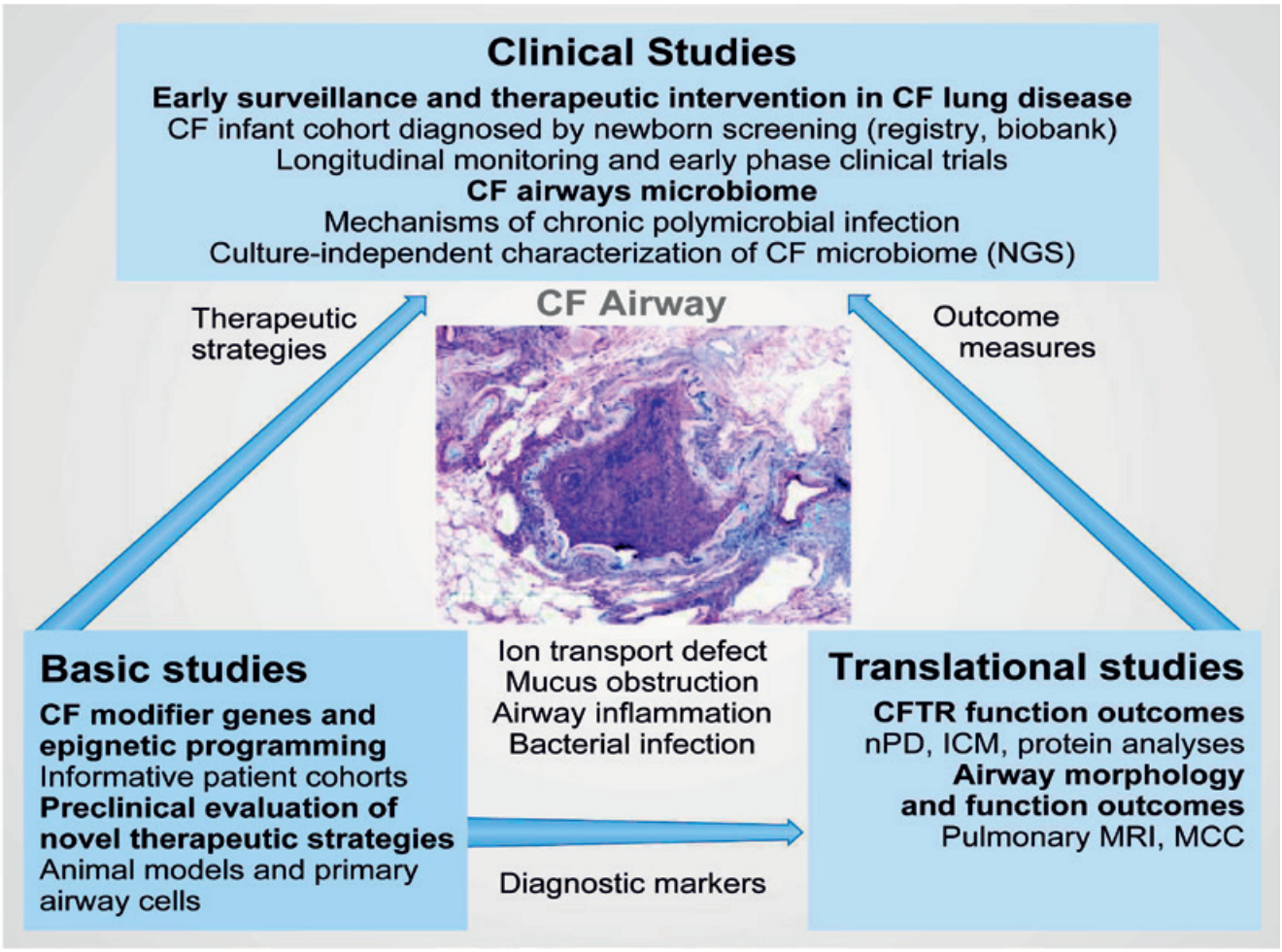
Highlighted Publications

1. Röpcke S, Holz O, Lauer G, Müller M, Rittinghausen S, Ernst P, Lahu G, Elmlinger M, Krug N, Hohlfeld JM. Repeatability of and Relationship between Potential COPD Biomarkers in Bronchoalveolar Lavage, Bronchial Biopsies, Serum, and Induced Sputum. PLoS One. 2012;7(10):e46207.
2. Cockayne DA, Cheng DT, Waschki B, Sridhar S, Ravindran P, Hilton H, Kourteva G, Bitter H, Pillai SG, Visvanathan S, Müller KC, Holz O, Magnussen H, Watz H, Fine JS. Systemic biomarkers of neutrophilic inflammation, tissue injury and repair in COPD patients with differing levels of disease severity. PLoS One. 2012;7(6):e38629.
3. Waschki B, Spruit MA, Watz H, Albert PS, Shrikrishna D, Groenen M, Smith C, Man WD, Tal-Singer R, Edwards LD, Calverley PM, Magnussen H, Polkey MI, Wouters EF. Physical activity monitoring in COPD: compliance and associations with clinical characteristics in a multicenter study. Respir Med. 2012 Apr;106(4):522-30.
4. Schleede S, Meinel FG, Bech M, Herzen J, Achterhold K, Potdevin G, Malecki A, Adam-Neumair S, Thieme SF, Bamberg F, Nikolaou K, Bohla A, Yildirim AÖ, Loewen R, Gifford M, Ruth R, Eickelberg O, Reiser M, Pfeiffer F. Emphysema diagnosis using X-ray dark-field imaging at a laser-driven compact synchrotron light source. Proc Natl Acad Sci U S A. 2012 Oct 30;109(44):17880-5.
5. Annoni, R., T. Lanças, R. Yukimatsu Tanigawa, M. de Medeiros Matsushita, S. de Morais Fernezlian, A. Bruno, L. Fernando Ferraz da Silva, P.J. Roughley, S. Battaglia, M. Dolhnikoff, P.S. Hiemstra, P.J. Sterk, K.F. Rabe and T. Mauad. 2012. Extra-cellular matrix composition in COPD. The European respiratory journal: official journal of the European Society for Clinical Respiratory Physiology. 40:1362–73.

Cystic Fibrosis

Disease Area Leaders	Prof. Dr. Marcus Mall (TLRC) Prof. Dr. Dr. Burkhard Tümmler (BREATH)
Participating DZL Partner Sites	BREATH, UGMLC, TLRC, ARCN
Number of Participating DZL Faculty	17

Cystic fibrosis (CF) is the most common genetically determined, early onset and still lethal form of chronic obstructive lung disease and affects approximately 1:2500 newborns in Caucasian populations. With improvements in symptomatic therapies and standardized CF care, the median survival of CF patients in Germany has increased to approximately 40 years; however, there are currently no therapies available that target CF lung disease at its root cause. The overall aim of the DZL CF research program is to advance the current understanding of the pathogenesis of CF lung disease and to use this knowledge to improve CF diagnostics, develop more sensitive tools for monitoring of disease activity, and develop novel strategies for effective prevention and therapy of CF lung disease.



Goals Followed in 2012 – Cystic Fibrosis

Goal 1 – Basic CF Research: From Modifiers to Novel Therapeutic Targets

- Genetic modifiers of CF Lung Disease
  - Identification of disease modifying genes in a mouse model of CF lung disease
- Epigenetic Programming of CF Lung Disease
  - Sequencing of immunoglobulin and T-cell receptor genes in monozygotic (identical) twins with CF
- Preclinical evaluation of mucolytic and anti-inflammatory treatment strategies
  - Preclinical evaluation of rehydrating and mucolytic strategies (hypertonic saline, long-acting sodium channel blocker) in β ENaC overexpressing mice

Goal 2 – Translational CF Research: Biomarkers and Outcome Measures

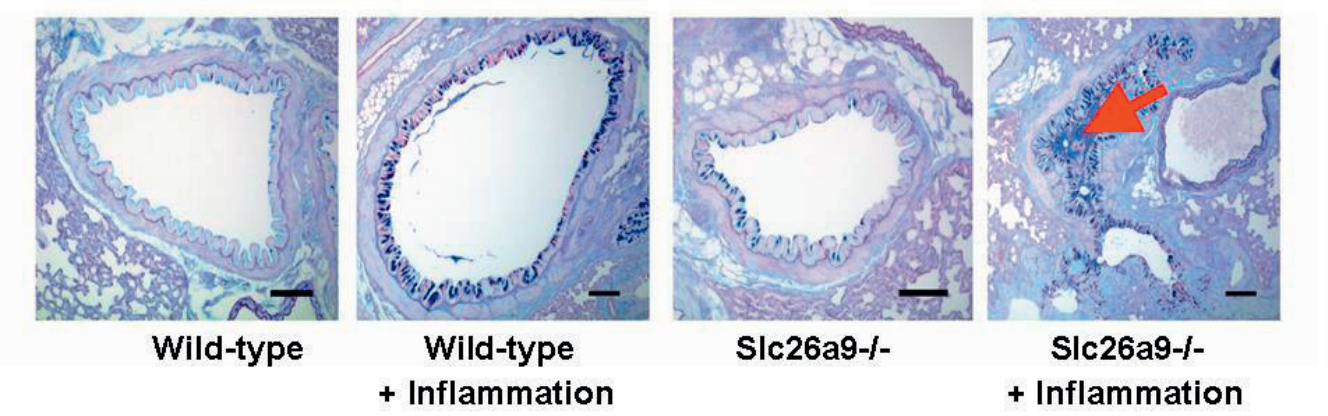
- Monitoring CFTR function ex vivo and in vivo
  - Standardization and evaluation of functional CFTR and biochemical analysis (nPD, ICM and CFTR immunoblots)
  - Evaluation and use of CFTR analysis (nPD, ICM and CFTR immunoblots) to improve the CF diagnosis
- Morphology and function of the respiratory system: pulmonary MRI and mucociliary clearance
  - Development and evaluation of morphological and functional MRI scores for non-invasive diagnostic monitoring of CF lung disease
  - Evaluation of lung MRI as a new endpoint in clinical trials (interventions: antibiotics, physiotherapy, inhaled mucolytics)
  - Application of lung MRI for longitudinal study of lung disease in CF newborn screening cohort

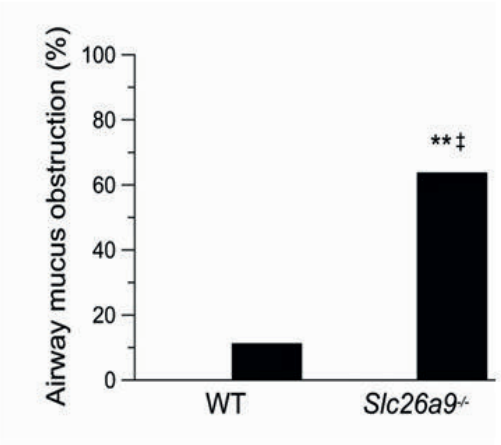
Goal 3 – Clinical CF Research Programs

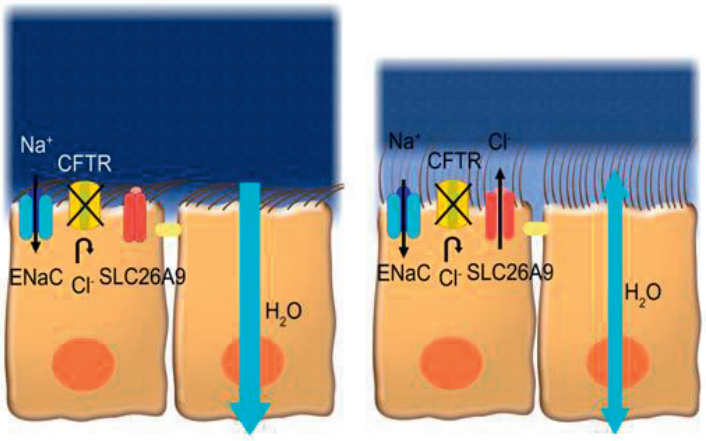
- Disease surveillance and therapeutic intervention in early CF lung disease
  - Establishment and validation of biochemical neonatal screening for CF
  - Building a cohort of newborn screening in early diagnosed CF patients
  - Longitudinal studies of early changes and spontaneous course of lung disease in the CF newborn screening cohort
- The Microbiome of CF Airways
  - Investigation of the microbiome of the upper and lower airways of CF patients using culture-independent methods before, during and after pulmonary exacerbation

2012 Research Highlights – Cystic Fibrosis

Research Highlight #1:

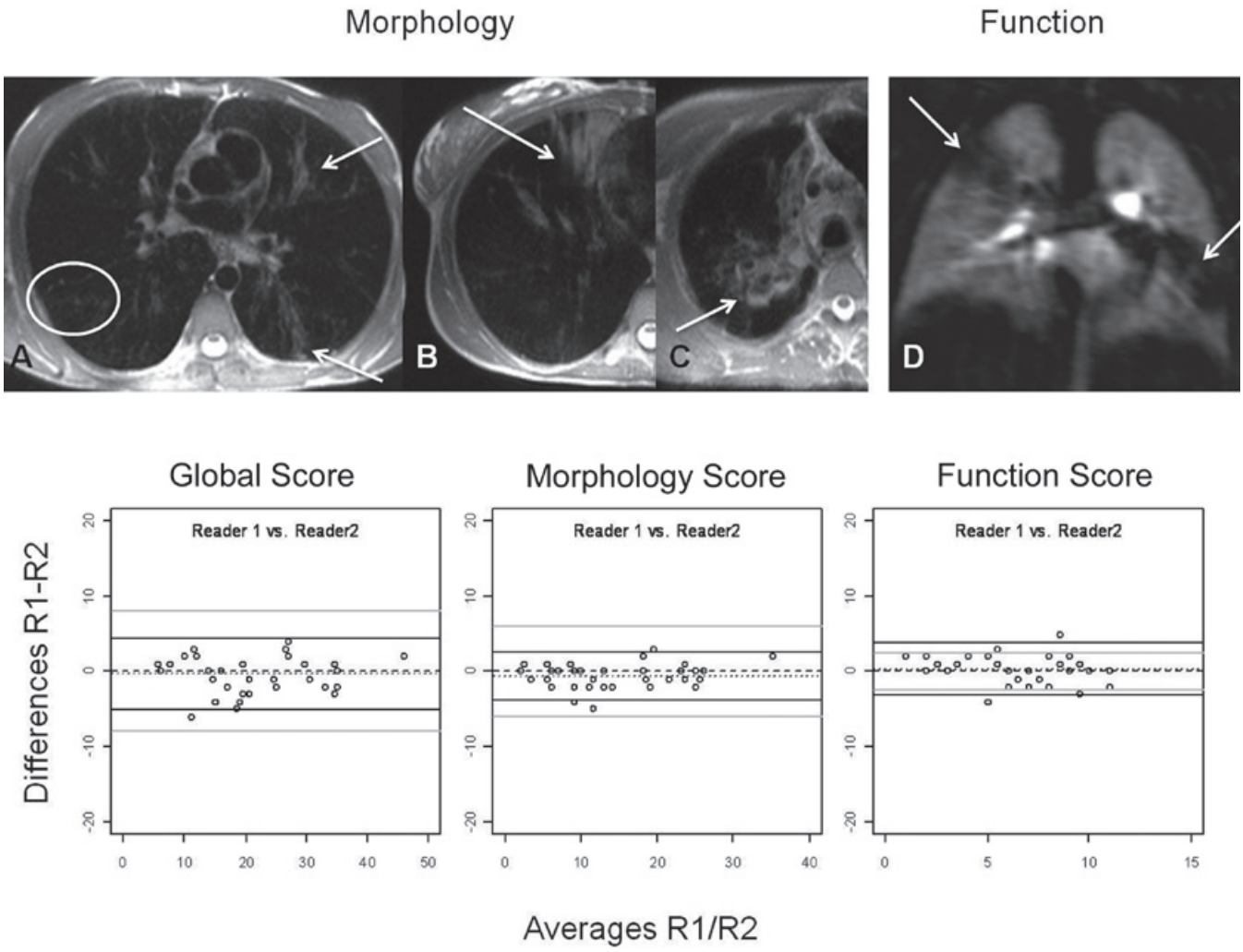






Airway surface dehydration causes mucociliary dysfunction and mucus plugging in cystic fibrosis (CF) lung disease. Alternative chloride channels have the potential to compensate for defective CFTR-mediated secretion of salt and water causing airway surface dehydration, and may thus circumvent the basic defect underlying chronic lung disease in patients with CF. In studies in normal mice (wild-type) and mice that lack the novel Slc26a9 chloride channel (Slc26a9-/-), we demonstrated that activation of this alternative channel prevents mucus plugging in airway inflammation. These results identified Slc26a9 as a novel therapeutic target for cystic fibrosis lung disease (J Clin Invest 2012; 122: 3629-34).

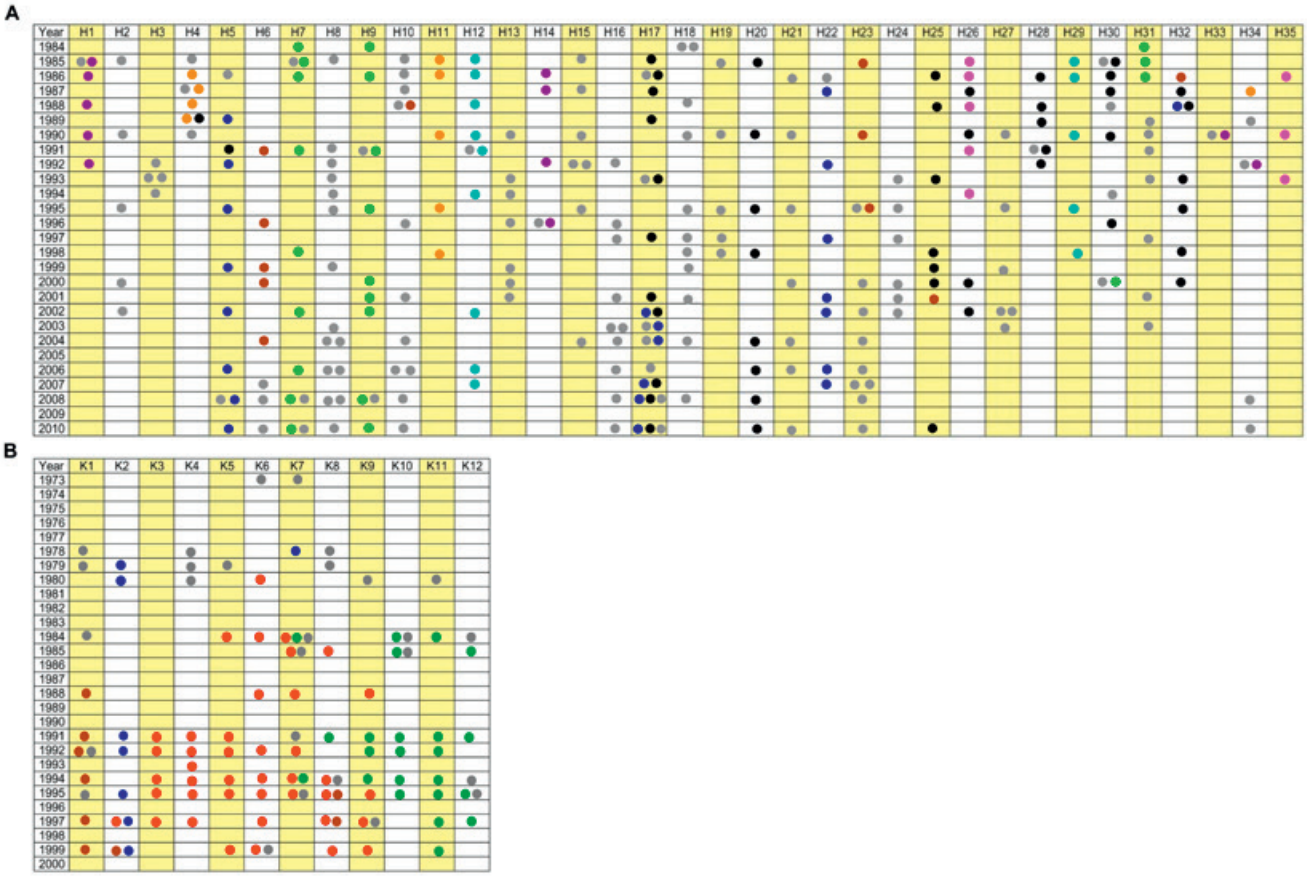
Research Highlight #2:



Recent computed tomography (CT) studies demonstrated that structural lung disease starts early in infants and young children with cystic fibrosis (CF), often even in the absence of respiratory symptoms. However, the use of CT for lifelong follow-up is restricted by cumulative radiation dose, highlighting the need for non-invasive detection and monitoring of CF lung disease. We therefore developed and evaluated Magnetic Resonance Imaging (MRI) of the lungs including a dedicated scoring system for a structured semi-quantitative assessment of structural and functional abnormalities in CF lung disease. This dedicated MRI score is now available for non-invasive monitoring and as an endpoint in clinical trials without radiation exposure (Eur J Radiol 2012;81:1321-9).

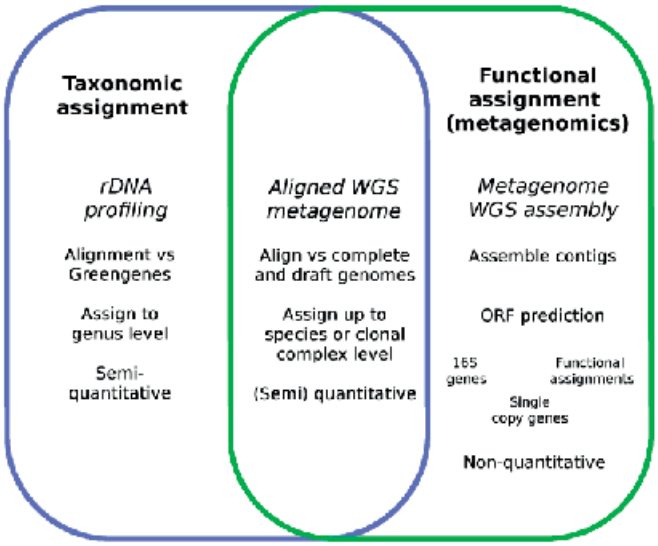
Research Highlight #3:

Molecular epidemiology of chronic airway infections with Pseudomonas aeruginosa in individuals with cystic fibrosis (CF) seen at the CF clinics in Hannover (A) and Copenhagen (B). Bacterial clones that are abundant in environment and disease are colored. Most patients at the Hannover clinic were chronically colonized with their initially acquired clone, whereas superinfection led to the spread of two dominant clones (green and red) at the Copenhagen clinic.



(with permission from PLoS One 2012;7:e50731)

Research Highlight #4:



(with permission from Environmental Microbiology (2013) 15(1), 1-5)

The analysis of the microbial communities in cystic fibrosis airways can be performed by alignment (blue) or assembly (green) of sequence reads. We developed wet lab protocols and a software pipeline for whole metagenome shotgun (WGS) sequencing. WGS allows a functional assessment of the gene content of the community and may provide information about the composition of the community up to the level of clonal complexes.

Number of papers published by DZL Faculty in 2012 – Disease Area Cystic Fibrosis: 21

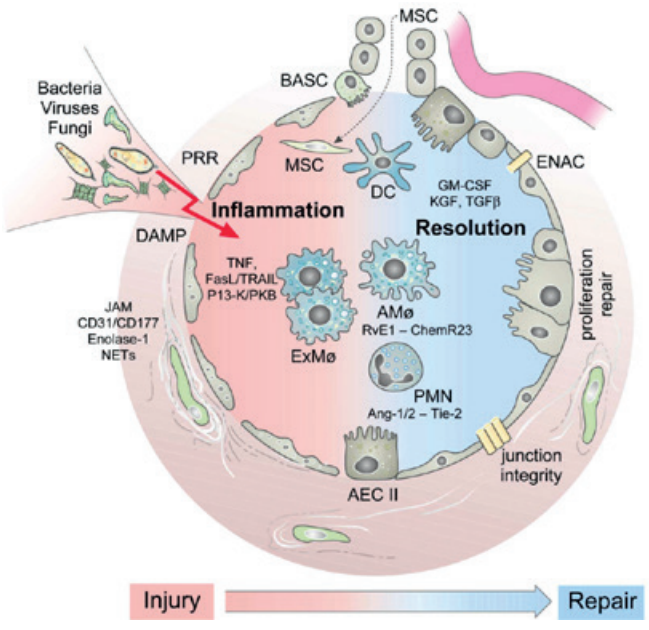
Highlighted Publications - 2012

1. Anagnostopoulou P, Riederer B, Duerr J, Michel S, Binia A, Agrawal R, Liu X, Kalitzki K, Xiao F, Chen M, Schatterny J, Hartmann D, Thum T, Kabesch M, Soleimani M, Seidler U, Mall MA. SLC26A9-mediated chloride secretion prevents mucus obstruction in airway inflammation. J Clin Invest 2012;122:3629-3634.
2. Eichinger M, Optazaite DE, Kopp-Schneider A, Hintze C, Biederer J, Niemann A, Mall MA, Wielputz MO, Kauczor HU, Puderbach M. Morphologic and functional scoring of cystic fibrosis lung disease using MRI. Eur J Radiol 2012;81:1321-1329.
3. Cramer N, Wiehlmann L, Ciofu O, Tamm S, Høiby N, Tümmler B. Molecular epidemiology of chronic Pseudomonas aeruginosa airway infections in cystic fibrosis. PLoS One. 2012;7:e50731.
4. 2012 Nov 28. PubMed PMID: 23209821; PubMed Central PMCID: PMC3508996.Wiehlmann L, Cramer N, Ulrich J, Hedtfeld S, Weissbrodt H, Tümmler B. Effective prevention of Pseudomonas aeruginosa cross-infection at a cystic fibrosis centre - results of a 10-year prospective study. Int J Med Microbiol. 2012;302:69-77.
5. Johannesson B, Hirtz S, Schatterny J, Schultz C, Mall MA. CFTR Regulates Early Pathogenesis of Chronic Obstructive Lung Disease in βENaC-Overexpressing Mice. PLoS ONE 2012;7:e44059.
6. van Barneveld A, Zander I, Hyde R, Länger F, Simon A, Krüger M, Ballmann M, Derichs N, Tümmler B. Immunochemical analysis of mutant CFTR in lung explants. Cell Physiol Biochem 2012; 30:587-95.

Pneumonia and Acute Lung Injury

Disease Area Leaders	Prof. Dr. Jürgen Lohmeyer (UGMLC) Prof. Dr. Tobias Welte (BREATH)
Participating DZL Partner Sites	ARCN, BREATH, UGMLC, TLRC, CPC-M
Number of Participating DZL Faculty	25

Acute lower respiratory tract infections represent an increasing public health problem worldwide, resulting in a disease burden greater than that of any other infection with mortality rates unchanged over the past 50 years. Likewise, the lack of any pharmacological treatment for the most devastating clinical course of pulmonary infection, the acute respiratory distress syndrome (ARDS), coupled with an unacceptably high mortality rate, underscores an urgent medical need for novel, effective therapeutic approaches. The DZL aims to dissect the molecular mechanisms underlying the sensing of, and signaling in response to microbial insult and inflammatory infiltration with the aim of developing targeted interventions to attenuate lung injury in pneumonia and ARDS.



Both microbial attack (bacteria, viruses, fungi) and non-microbial inflammatory injury (aspiration, toxic gases) may cause acute lung injury with severe respiratory failure. The goal of this Disease Area is to dissect the molecular mechanisms underlying the spreading of inflammatory events in the alveolar compartments, and to understand the cellular and molecular players driving resolution of inflammation and repair of alveolar integrity. Based on understanding these events, new therapeutic concepts are to be developed.

(AEC II – alveolar type II cells; AMø – alveolar macrophage; Ang – angeopoietin; BASC – bronchioalveolar stem cells; DAMP – damage-associated molecular patterns; DC – dendritic cell; ENAC – epithelial socium channel; ExMø – exudate macrophages; FasL – Fas-ligand; FGF – Fibroblast Growth Factor; GM-CSF - granulocyte macrophage colony-stimulating factor; JAM – junctional adhesion molecule; BETs – neutrophil extracellular traps; KGF – keratinocyte growth factor; MSC – mesenchymal stem cell; PI3K – phosphatidylinositol-3 kinase; PKB – protein kinase B; PNM – neutrophils; PRR – pattern recognition receptors; RvE1 – resolvin; TGF – transforming growth factor; TNF – tumor necrosis factor; TRAIL – TNF-related apoptosis inducing ligand)

Goals Followed in 2012 – Pneumonia and Acute Lung Injury

Goal 1 - Sensing Microbial and Inflammatory Lung Attack

- Basic Research
  - Characterization of pulmonary pattern recognition molecules for pathogen / host ligands
  - Evaluation of the role of 'Brush cells' as sensors of microbial pathogens in the bronchial tree
- Translational Research
  - Characterization of pulmonary host defense of wild type and C-type Lectin receptor (CLR) deficient mice in focal pneumonia
  - Employment of Pattern Recognition Receptors (PPR) on dendritic cells for immunomodulation
- Clinical Research
  - Creation of BAL inflammatory profiles in pneumonia / ARDS patient cohorts

Goal 2 - Lung Innate Immune Responses

- Basic Research
  - Analysis of pathogen-specific pulmonary recruitment of inflammatory cells in pneumonia/ARDS
- Translational Research
  - Establishment of the lung-specific transient over-expression of macrophage-related chemokines in the mouse

Goal 3 – Resolution of Lung Inflammation, Lung Barrier Protection and Regeneration

- Basic Research
  - Investigation of the influence of the pulmonary inflammation processes by local hypoxia, endocrine signals and the type of ion transport
  - Establishment of intervention strategies to restore damaged inflammatory ion transport and improve endo / epithelial barrier function
- Translational Research
  - Analysis of the anti-inflammatory, pro-resolution and alveolar repair mediating capacity of mesenchymal stem cells
- Clinical Research
  - Performing a dose-escalating pilot study with chemically defined lipid infusions in critically ill patients (NCTC1146821, EudraCT 2010-021018-49)

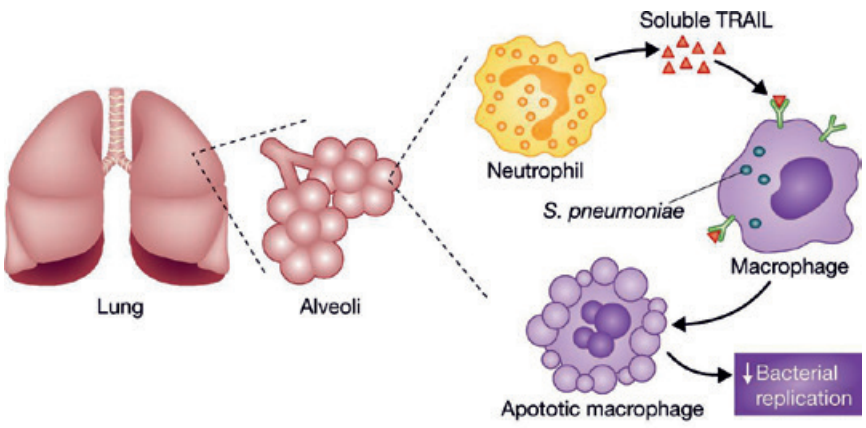
Goal 4 – Preventive Strategies

- Establishing a pneumococcal colonisation / invasion model in the mouse with normal versus impaired mucociliary clearance (ENaC tg)

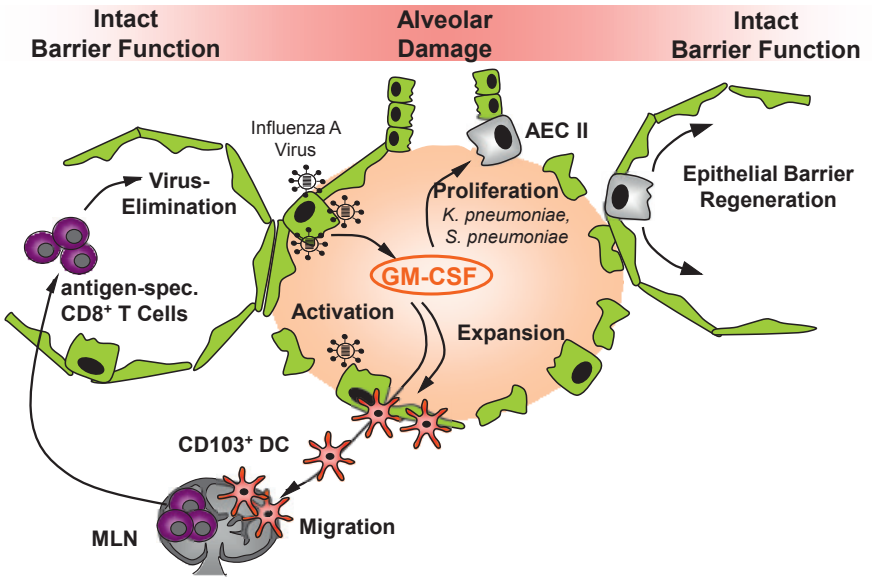
2012 Research Highlights – Pneumonia and Acute Lung Injury

Research Highlight #1:

Soluble TNF-related apoptosis-inducing ligand (TRAIL) was found to play a central role in the control of bacterial spreading in pneumococcal pneumonia in mice. Therapeutic application of TRAIL improved lung protective immunity against S. pneumonia, reduced the bacterial load in the alveolar compartment, and enhanced survival (Steinwede et al., J Exp Med 209: 1937, 2012). Current research probes the suitability of this approach for better treatment of human bacterial pneumonia. (Figure ©Benedict and Ware 2012. Originally published in J Exp Med. doi 10.1084/jem.20122235)



Research Highlight #2:

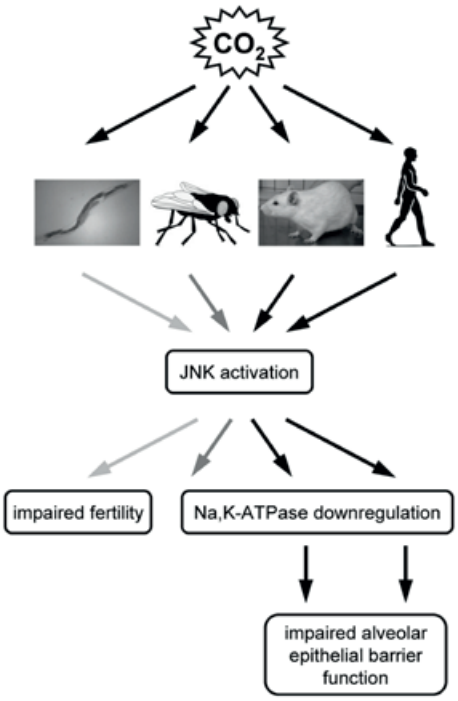


Influenza induced pneumonia is characterized by viral replication in the alveolar compartment, severe epithelial injury, and loss of alveolar epithelial barrier function. Therapeutic application of GM-CSF enhances dendritic cell and T cell based anti-viral immunity and fosters epithelial regeneration and restoration of barrier integrity. Secondary infection with bacterial agents is reduced (Unkel et al., J Clin Invest 122:3652, 2012).

(AEC II – alveolar type II cells; DC – Dendritic Cell; ; GM-CSF - granulocyte macrophage colony-stimulating factor; MLN - mediastinal lymph node)

Research Highlight #3:

Discovery of evolutionary conserved CO2-induced effects: Elevated CO2 levels rapidly activate Jun Kinase (JNK) in C. elegans, Drosophila, rat lungs and human alveolar epithelial cells. In C. elegans (light grey arrows) the CO2-induced JNK activation leads to impaired fertility. In Drosophila (dark gray arrows) and in the rat and human alveolar epithelium (black arrows) the hypercapnia-induced JNK activation decreases Na,K-ATPase membrane stability leading to impaired alveolar epithelial barrier function in mammals. This basic mechanism may contribute to lung function abnormalities in hypercapnic patients, such as severe COPD, kyphoscoliosis and respiratory muscle dysfunction, and under conditions of permissive hypercapnia in mechanically ventilated ARDS patients (Figure with permission from PLoS ONE Vadasz et al 7:e46696, 2012)



Number of papers published by DZL Faculty in 2012 - Pneumonia and Acute Lung Injury: 41

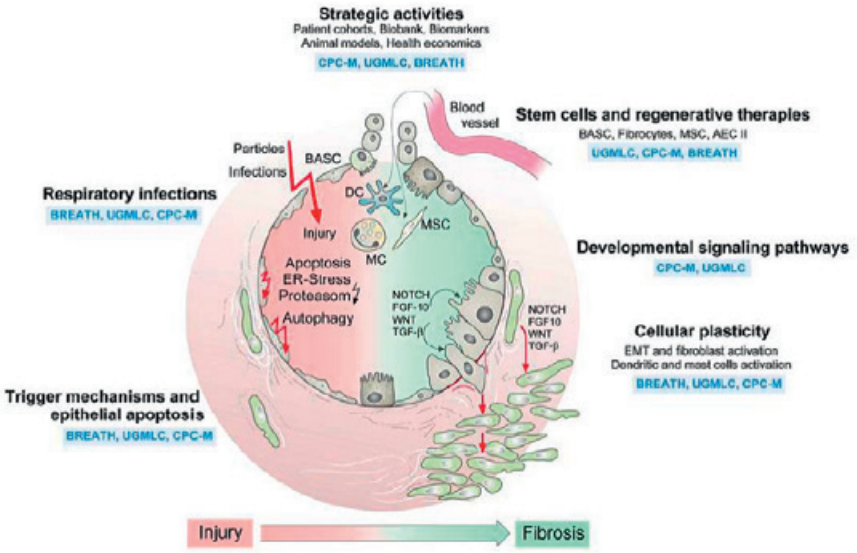
Highlighted Publications

1. Buchäckert Y, Rummel S, Vohwinkel CU, Gabrielli NM, Grzesik BA, Mayer K, Herold S, Morty RE, Seeger W, Vadász I. Megalin mediates transepithelial albumin clearance from the alveolar space of intact rabbit lungs. J Physiol. 590(20):5167-5181, 2012.
2. Saffarzadeh M, Juenemann C, Queisser MA, Lochnit G, Barreto G, Galuska SP, Lohmeyer J, Preissner KT. Neutrophil extracellular traps directly induce epithelial and endothelial cell death: a predominant role of histones. PLoS One 2012; 7:1-14 (e32366).
3. Steinwede K, Henken S, Bohling J, Maus R, Ueberberg B, Brumshagen C Brincks EL, Griffith TS, Welte T, Maus UA. TNF-related apoptosis-inducing ligand (TRAIL) exerts therapeutic efficacy for the treatment of pneumococcal pneumonia in mice. J Exp Med 209:1937-1952, 2012.
4. Unkel B, Hoegner K, Clausen BE, Lewe-Schlosser P, Bodner J, Gattenloehner S, Janßen H, Seeger W, Lohmeyer J, Herold S. Alveolar epithelial cells orchestrate DC function in murine viral pneumonia. J Clin Invest 2012; 122:3652-64.
5. Vadász I, Dada LA, Briva A, Helenius IT, Sharabi K, Welch LC, Kelly AM, Grzesik BA, Budinger GR, Liu J, Seeger W, Beitel GJ, Gruenbaum Y, Sznajder JI. Evolutionary conserved role of c-Jun-N-terminal kinase in CO2-induced epithelial dysfunction. PLoS ONE. 7(10):e46696, 2012

Diffuse Parenchymal Lung Disease (DPLD)

Disease Area Leaders	Prof. Dr. Oliver Eickelberg (CPC-M) Prof. Dr. Andreas Günther (UGMLC)
Participating DZL Partner Sites	BREATH, UGMLC, TLRC, CPC-M
Number of Participating DZL Faculty	31

Diffuse parenchymal lung diseases (DPLD) comprise more than 100 different entities, yet share similar pathomechanistic principles, including progressive fibrosis of the pulmonary interstitium, distortion of normal lung architecture, and respiratory failure. Fibrotic alterations in DPLD can occur secondary to acute or chronic lung injury, provoked by chemotherapy, toxin inhalation, collagen vascular disease, ventilation, or as an idiopathic entity (idiopathic interstitial pneumonia). Most DPLD exhibit a poor prognosis in the absence of medical treatment. One form of DPLD, Idiopathic Pulmonary Fibrosis (IPF), in particular, displays a progressive, devastating, and ultimately fatal course of disease which is largely resistant to medical treatment. As such, lung transplantation remains the only therapeutic intervention with a known survival benefit for IPF patients. Due to the urgent unmet medical need, the DZL DPLD program primarily focuses on IPF. The DZL aims to identify novel molecular concepts and targets for the treatment of IPF, with the expectation that such discoveries will be transferable to positive outcomes for patients with other forms of DPLD.



Depicted are the key goals of the Disease Area DPLD. In addition to strategic activities aiming to establish novel models of lung fibrosis and to facilitate access to human fibrotic tissues, the DZL disease area DPLD is actively performing research in the field of initial trigger mechanisms and relevant second hits such as respiratory infections. DZL scientists are also clarifying the role of the reactivation of developmental signaling pathways, investigating the importance of cellular plasticity for the development of the fibrotic tissue, and scrutinizing the therapeutic role of cell-based therapies in the field of DPLD.

(AEC II – alveolar type II cells ; BASC – bronchioalveolar stem cells; DC – dendritic cell; FGF – Fibroblast Growth Factor; MC – mast cell; MSC – mesenchymal stem cell; TGF – transforming growth factor)

Goals Followed in 2012 – DPLD

Goal 1 – Strategic Activities

- Creation of a DZL-wide mutually shared patient registry
- Establishment of additional animal models for lung fibrosis and bronchopulmonary dysplasia (BPD)
- Evaluation of costs, health-related quality of life, and economic viability of new therapeutic approaches

Goal 2 – Trigger Mechanisms of DPLD and Epithelial Apoptosis

- The role of ER stress signaling pathways in lung fibrosis
- The role of proteasome function for ER-stress induced apoptosis in IPF
- Defective lysosomal transport and autophagy in lung fibrosis

Goal 3 – Developmental Signaling Pathways in DPLD

- Preparation and analysis of transgenic animal models of epithelial cell-lineage tracing
- Identification of critical cell type-specific components of the FGF, Wnt and Notch signaling in DPLD

Goal 4 – Cellular Plasticity and Crosstalk in DPLD

- Description of the timing and pathological relevance of epithelial-mesenchymal transition in IPF
- Identification of key molecules in the remodeling of extracellular matrix in IPD and BPD
- Evaluation of appropriate indicators / variables that allow early diagnosis of changes in the lungs (to prevent the development of BPD)

Goal 5 – Respiratory Infections in Lung Fibrosis

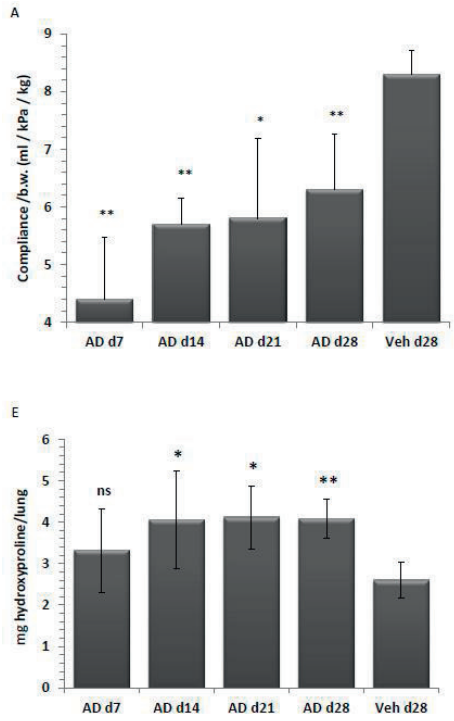
- The impact of Gram + / Gram - bacteria on onset and progression of pulmonary fibrosis
- Elucidation of the influence of pulmonary fibrosis on the clearance of pathogens from the lungs

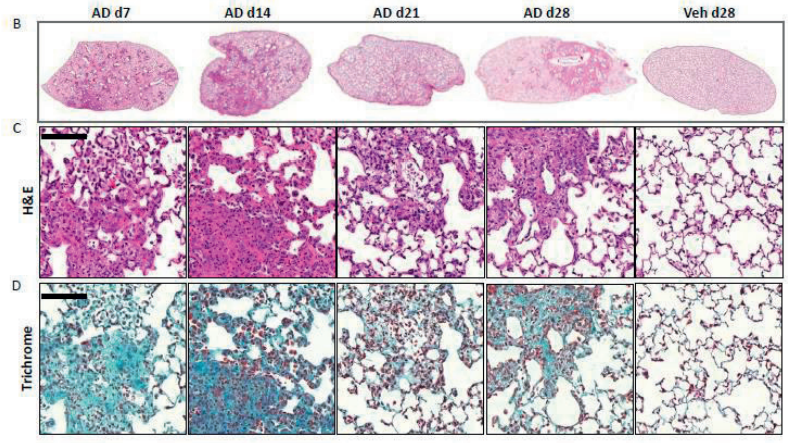
Goal 6 – Stem/Progenitor Cells and Regenerative Therapies in DPLD

- Characterization of the distribution and function of broncho-alveolar stem cells
- Evaluation of the suitability of fibrocytes as predictive biomarkers in DPLD
- Identification and characterization of appropriate cell populations offering for “stem cell treatment”; assessment of optimal application strategies

2012 Research Highlights – DPLD

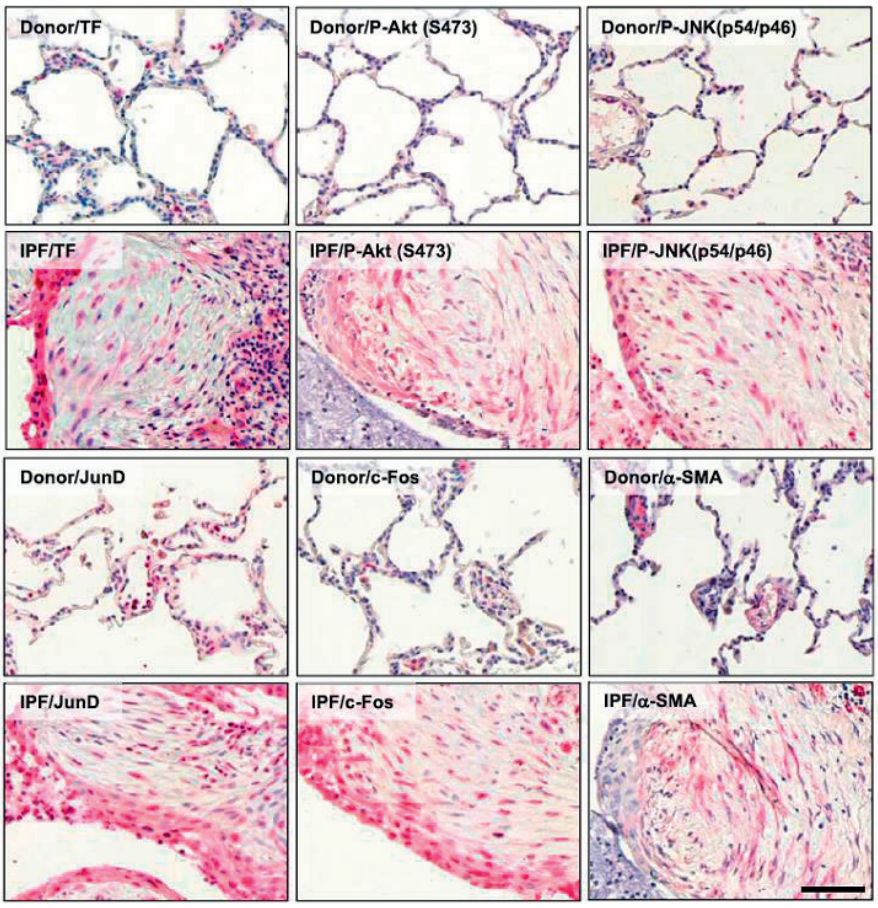
Research Highlight #1:





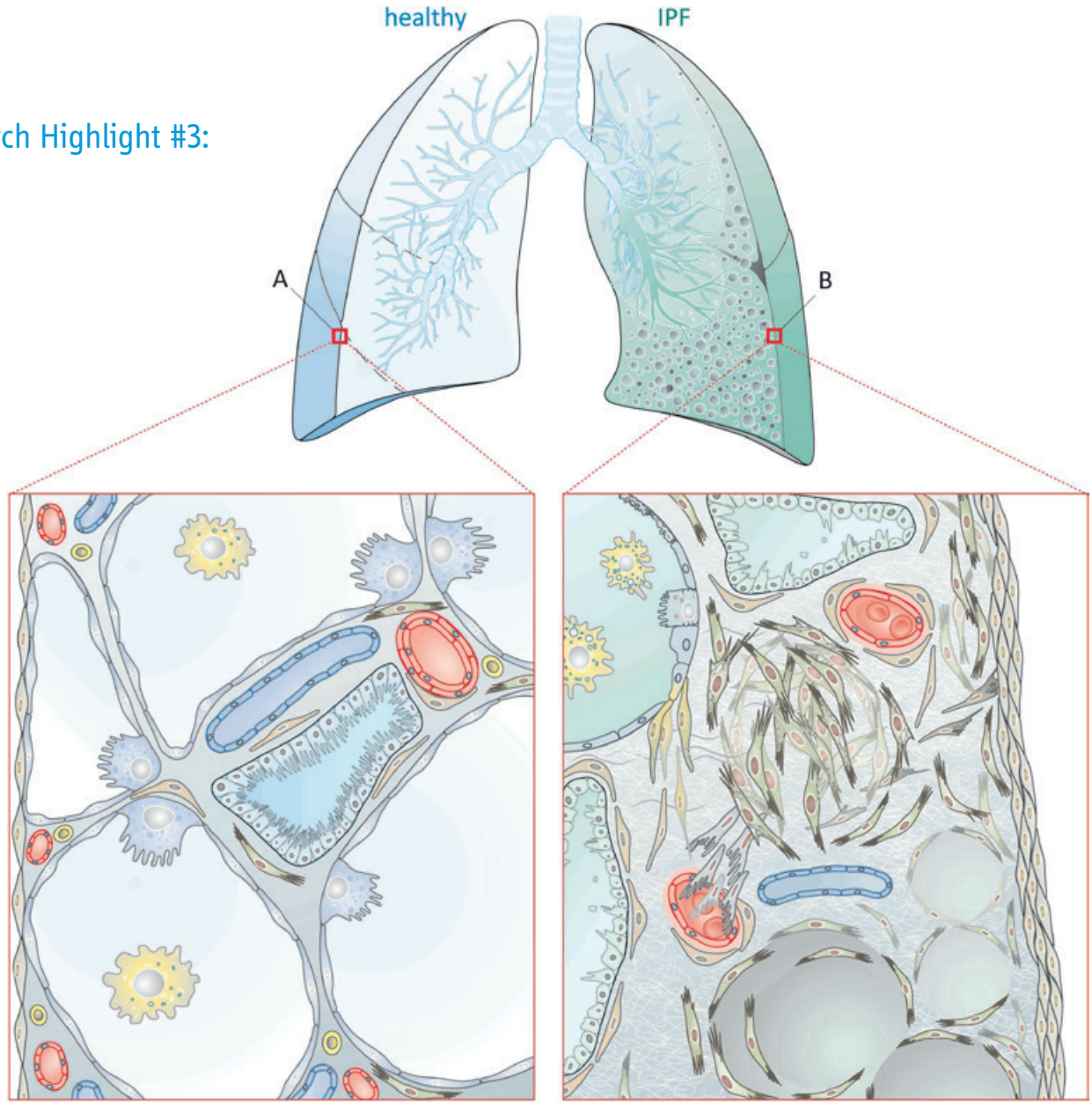
A novel model of amiodarone induced lung fibrosis in mice. Amiodarone (Ad) is a widely used and highly efficient antiarrhythmic drug. Due to its amphiphilic nature, amiodarone targets the lysosomal compartment of human cells, where its concentration is likely 500 fold increased compared to serum. 2-4% of chronically treated patients develop a severe lung fibrosis, with a complex spectrum of histopathological appearances including usual interstitial pneumonia (UIP), which is also found in IPF. DZL scientists have developed a novel mouse model of lung fibrosis based on the transbronchial application of amiodarone. In this model, massive lung fibrosis develops as early as day 7, as is evident from lung compliance (upper left), hydroxyproline content of the lung (lower left) and histology (upper right), and continues to be visible until d28. Follow up research in this model provided evidence that – like in IPF – a massive apoptosis of alveolar type II cells is encountered, in part due to inappropriate activation of autophagy pathways. Inflammation is not a predominant feature in this model, again providing some similarity with human IPF (Mahavadi et al., unpublished data).

Research Highlight #2:



Regulation of procoagulant pathways by transforming growth factor-β1. In IPF patients, an increased expression of procoagulant factors and a shift of the hemostatic balance towards coagulation have been observed early on, including the expression of the extrinsic pathway compound "tissue factor" (TF). However, the molecular mechanisms responsible for the regulation of TF expression under profibrotic conditions have not been assessed, especially in lung fibroblasts. We found that the key profibrotic growth factor "transforming growth factor-β1" (TGF-β1) markedly enhanced TF expression in primary human lung fibroblasts (HLFs), whereas platelet-derived growth factor (PDGF)-BB and IGF (insulin-like growth factor)-1 showed only a moderate effect, and PDGB-CC exerted no effect. TGF-β1-induced TF expression correlated with its elevated cell-surface activity; it required de novo gene transcription and protein synthesis. Our studies revealed that TGF-β1 exposure results in an activation of the PI3K/JNK/Akt and the AP-1 signalling pathways, which seem to synergize to induce TF expression in human lung fibroblasts in vitro. Accordingly, strong immunoreactivity for phosphorylated Akt (top two lines, middle) and JNK (top two lines, right) as well as c-Fos (lower two lines, middle) and JunD (lower two lines, left) was observed in fibroblasts and myofibroblasts (indicated by a-SMA staining; lower two lines, right) alongside with TF expression (top two lines, left) in IPF (second and fourth line) versus control ("donor", first and third line) lungs (Reprinted with permission of the American Thoracic Society. Copyright © 2013 American Thoracic Society. Wygrecka et al., 2012. TGF-β1 induces tissue factor expression in human lung fibroblasts in a PI3K/JNK/Akt-dependent and AP-1-dependent manner. 47:614-27. Official Journal of the American Thoracic Society.)

Research Highlight #3:



Definitive influence of cellular environment on tissue remodeling during fibrosis. The lung contains more than 40 different cell types, yet most of the increased extracellular matrix that is deposited in idiopathic pulmonary fibrosis is ascribed to activated myofibroblasts in fibroblast foci. These lesions do not arise in healthy lungs, yet are frequently identified in IPF biopsy samples and their number correlates with survival. There is much evidence in the literature that myofibroblasts originate from several cellular sources in the lung including alveolar epithelial cells or mesothelial cells (via epithelial-mesenchymal or mesothelial-mesenchymal transition, the first in current controversy); from local mesenchymal cells, such as fibroblasts or pericytes (via proliferation and invasion); or from circulating progenitor cells (such as fibrocytes, via recruitment, invasion, and activation). A detailed characterization of mesenchymal subtypes should help clarify their origin and lead to identification of novel markers for detection, thus elucidating their precise role in the diseased lung.

Number of papers published by DZL Faculty in 2012 – Disease Area DPLD: 20

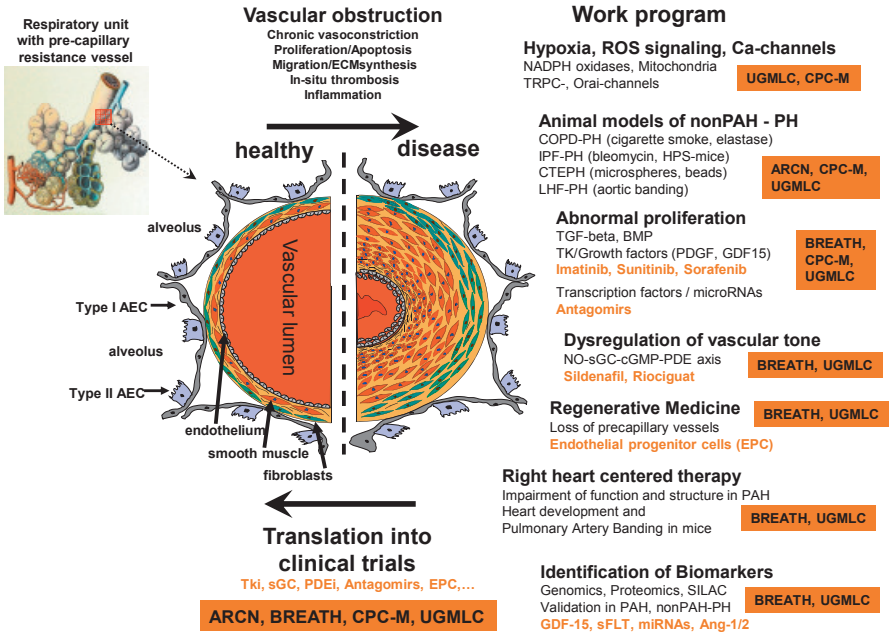
Highlighted Publications

1. El Agha E, Al Alam D, Carraro G, MacKenzie B, Goth K, De Langhe SP, Voswinckel R, Hajihosseini MK, Rehan VK, Bellusci S. Characterization of a novel fibroblast growth factor 10 (Fgf10) knock-in mouse line to target mesenchymal progenitors during embryonic development. PLoS One. 2012;7(6):e38452.
2. Fernandez IE, Eickelberg O. New cellular and molecular mechanisms of lung injury and fibrosis in idiopathic pulmonary fibrosis. Lancet. 2012; Aug 18;380(9842):680-8. doi: 10.1016/S0140-6736(12)61144-1.
3. Krauss-Etschmann S, Bush A, Bellusci S, Brusselle GG, Dahlén SE, Dehmel S, Eickelberg O, Gibson G, Hylkema MN, Knaus P, Königshoff M, Lloyd CM, Macciarini P, Mailleux A, Marsland BJ, Postma DS, Roberts G, Samakovlis C, Stocks J, Vandesompele J, Wjst M, Holloway J. Of flies, mice and men: a systematic approach to understanding the early life origins of chronic lung disease. Thorax. 2013 Apr;68(4):380-4.
4. Rock J, Königshoff M. Endogenous lung regeneration: potential and limitations. Am J Respir Crit Care Med. 2012; Dec 15;186(12):1213-9. doi: 10.1164/rccm.201207-1151PP. Epub 2012 Sep 20.
5. Wygrecka M, Zakrzewicz D, Taborski B, Didiasova M, Kwapiszewska G, Preissner KT, Markart P. TGF-β1 induces tissue factor expression in human lung fibroblasts in a PI3K/JNK/Akt-dependent and AP-1-dependent manner. Am J Respir Cell Mol Biol. 2012 Nov;47(5):614-27.
6. Günther A, Korfei M, Mahavadi P, von der Beck D, Ruppert C; Markart P. Unravelling the progressive pathophysiology of idiopathic pulmonary fibrosis. Eur Respir Rev 2012; 21:152-160

Pulmonary Hypertension

Disease Area Leaders	Prof. Dr. Hossein Ardeschir Ghofrani (UGMLC) Prof. Dr. Dr. Friedrich Grimminger (UGMLC) Prof. Dr. Marius Höper (BREATH) Prof. Dr. Ralph Schermuly (UGMLC)
Participating DZL Partner Sites	ARCN, BREATH, UGMLC, CPC-M
Number of Participating DZL Faculty	34

Pulmonary hypertension (PH) is a disease of the pulmonary vasculature, which leads to shortness of breath, dizziness, fainting, and ultimately right heart failure. Five PH subclasses have been defined and all variants of PH together are estimated to affect up to 100 million people worldwide. The vascular pathology of PH is characterized by pulmonary vasoconstriction and by abnormal ("pseudo-malignant") remodeling processes of all vessel layers. Vascular smooth muscle cell (SMC) proliferation is a prominent feature in virtually all PH entities. These remodeling processes result in severe loss of cross-sectional area, vascular pruning, and a concomitant increase in right ventricular afterload. Current PH therapy provides symptomatic relief and improves prognosis, but falls short as to reestablishment of structural and functional lung vascular integrity as a basis for handicapped-free long-term survival. The restoration of physiological vascular structure and function (reverse remodeling) represents the major therapeutic goal of the DZL PH team.



Vascular Remodelling and Reverse Remodelling in Pulmonary Hypertension. Putative therapeutic targets are indicated. (NO, nitric oxide; sGC, soluble guanylate cyclase; cGMP, cyclic guanosine monophosphate; PDE, phosphodiesterase; TGF, (transforming growth factor)-b; BMP, bone morphogenetic protein; TK, tyrosine kinase; PDGF, platelet-derived growth factor; EGF, epidermal growth factor; VEGF, vascular endothelial growth factor; EPC, endothelial progenitor cells; TRPC, transient receptor potential cation channels; NADPH, nicotinamide adenine dinucleotide phosphate; TKi, tyrosine kinase inhibitor; AEC, alveolar epithelial cells.)

Goals Followed in 2012 – Pulmonary Hypertension

Goal 1 – Basic Research in Pulmonary Hypertension – From Disease Genes To New Therapeutic Approaches

- Hypoxia, ROS signaling pathways and hypoxia-induced gene regulation in PH
  - Detection of ROS in isolated lungs and isolated smooth muscle cells before and after hypoxia
- Investigation of the mitochondrial respiratory chain and membrane potential and investigation of inhibitors
- New calcium (Ca2 +) influx pathways in pulmonary hypertension and vascular dysfunction
  - Investigation of the pathophysiological role of the TRP and the store-operated Orai channels
  - Investigation of calcium signaling pathways using patch-clamp and single-cell fluorescence imaging in combination with functional studies on endothelial cells and smooth muscle cells
- Animal models for non-PAH PH
  - Establishment of the transaortic banding model (TAC) to study PH due to left ventricular disease; testing of new substances and those already approved for PAH treatment

Goal 2 – Translational Pulmonary Hypertension Research

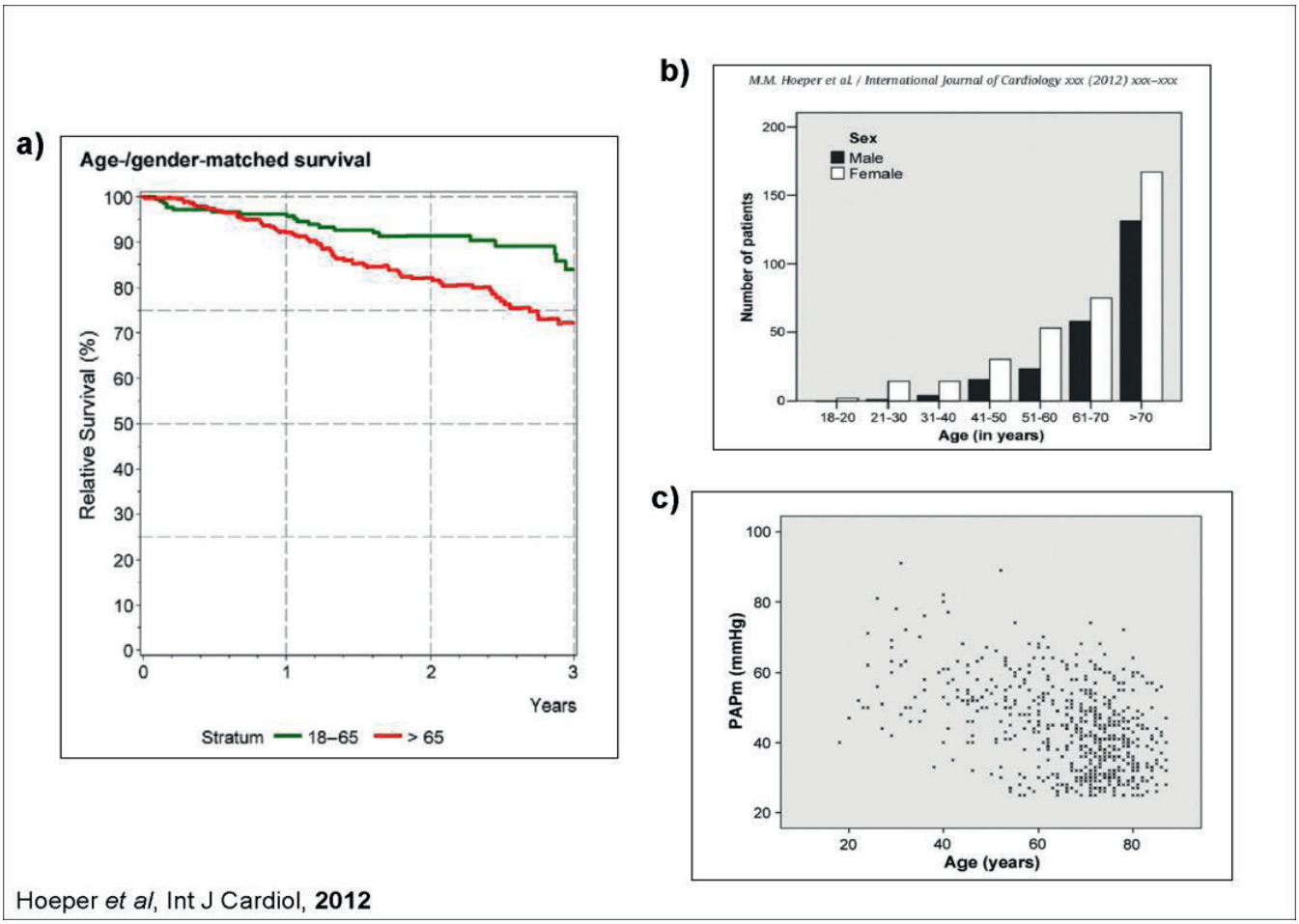
- Promotion of vascular remodeling in PH: transcription factors and receptor tyrosine kinases
  - Study of the expression profiles of various growth factors in experimental and clinical PH and non-PAH PH
  - Examination of the profile of expression of receptor tyrosine kinases in human and experimental PAH tissue
- Reverse remodeling by NO-guanylate cyclase-phosphodiesterase-axis
  - Investigation of sGC expression and activity of the various subunits and the signal connected molecules in experimental and clinical PH and non-PAH PH
  - Investigation of the therapeutic potential of DDAH in vitro and in vivo
  - Examination of the role of various PDE isoforms and their possible therapeutic potential for non-PAH PH (experimental and clinical)
- MicroRNAs and Antagomirs for the treatment of PH
  - Assessment of cell- and compartment-specific miRNA profiles in experimental PAH and non-PAH-PH models, and in human PAH tissue
- Endothelial progenitor cell (EPC)-based revascularization of the lung
  - Conduct investigations to increase the pro-angiogenic potential of EPCs by prestimulation with homing-promoting factors
  - Isolation of EPCs in from human peripheral blood; manipulation of these cells by pharmacological approaches and transfection technology
- Treatment of PH with a focus on the right heart
  - Analysis of the expression and the functional role of genes regulated in right heart failure in response to increased afterload

Goal 3 – Clinical Pulmonary Hypertension Research

- Non-hypothesis-based screen for new biomarkers
  - Identification of potential biomarkers for the assessment of pulmonary vascular resistance and the load of the right ventricle in CTEPH patients
- Phenotyping of different PH entities and correlation with biomarker candidates
  - Identification of potential biomarkers for the assessment of disease severity and treatment success; differentiation of the various PH subtypes

2012 Research Highlights – Pulmonary Hypertension

Research Highlight #1:

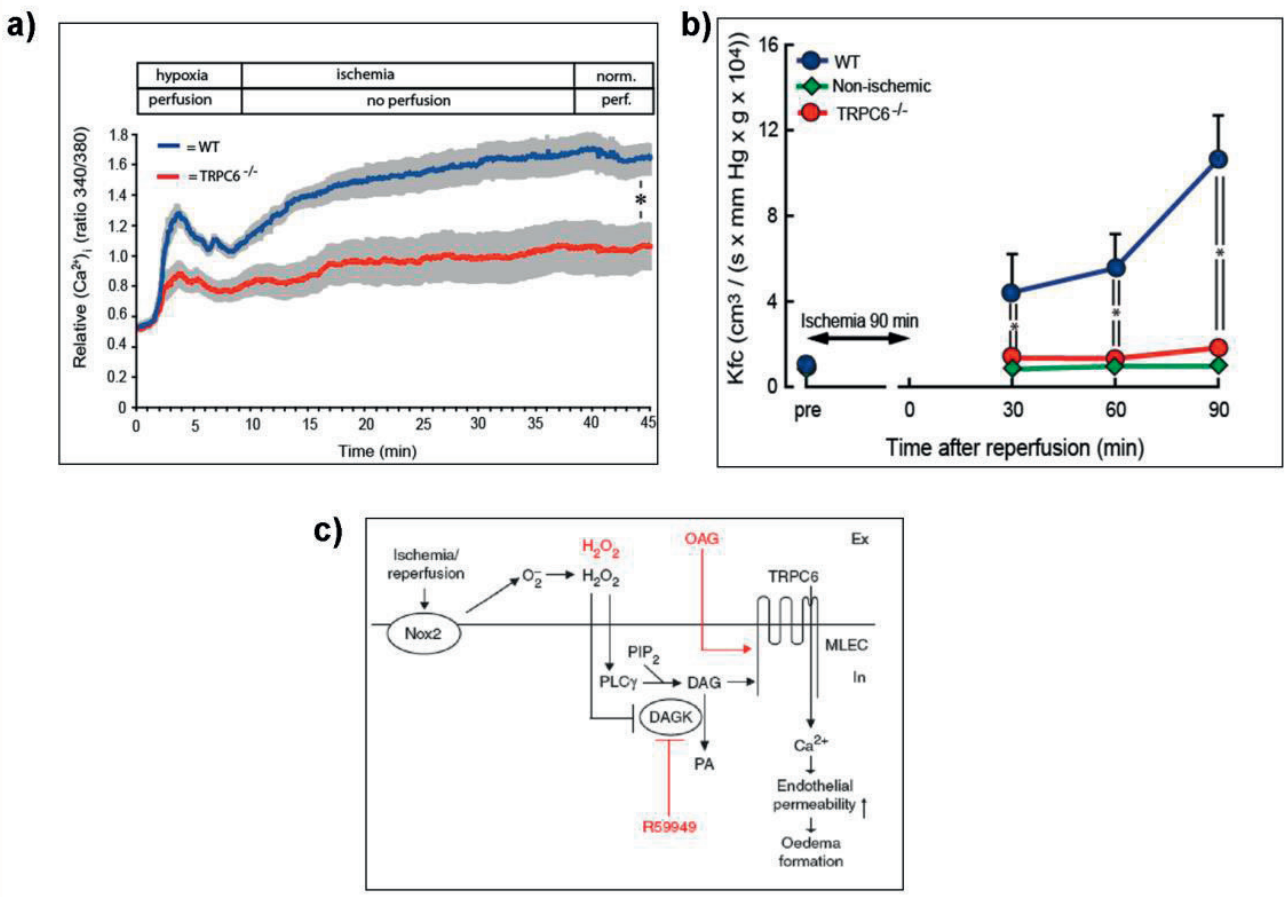


Hoeper *et al*, Int J Cardiol, **2012**

It has been previously accepted that idiopathic pulmonary arterial hypertension (IPAH) mostly affects younger females; however, a significant portion of older patients with IPAH has been recognized in recent years. Therefore, this clinical study aimed to describe the characteristics of such patients, focusing on survival, gender distribution and hemodynamics. Results revealed that IPAH was often diagnosed in elderly patients, and it was associated with increased age-adjusted mortality, compared to younger population. Furthermore, older patients had balanced gender (male-female) ratio, in comparison with younger patients. Finally, hemodynamic profile seemed to be different in elderly patients, and although they responded to pulmonary hypertension related therapy, the response was less good compared to younger population. Further clinical studies and profound characterization of elderly patients in the context of IPAH are required.

a) Age/gender-matched survival in younger (18–65 years) and elderly (>65 years) patients with idiopathic pulmonary arterial hypertension. b) Gender distribution of patients with idiopathic pulmonary arterial hypertension according to age. c) Correlation between age and mean pulmonary artery pressure (PAPm) at diagnosis. (Reprinted from International Journal of Cardiology, 168(2), Hoeper et al., Elderly patients diagnosed with idiopathic pulmonary arterial hypertension: Results from the COMPERA registry. Pages 871-880. Copyright 2013, with permission from Elsevier)

Research Highlight #2:



Weissmann *et al*, Nat Commun, **2012,** 3:649

Lung ischaemia-reperfusion-induced oedema (LIRE) is a severe medical condition that leads to pulmonary oedema induced by endothelial dysfunction. This study revealed that lungs from mice lacking nicotinamide adenine dinucleotide phosphate oxidase (Nox2y/-) or the classical transient receptor potential channel 6 (TRPC6-/-) are actually protected from LIRE development. Furthermore, endothelial cells from above mentioned deficient mice showed decreased ischaemia-induced Ca2+ influx, cellular shape alterations and impaired barrier function. Additionally, the generation of reactive oxygen species was fully abolished in Nox2y/- cells. Finally, we proposed a novel mechanism, as depicted in Figure c. As LIRE may severely compromise the life of the patients, our results clearly suggested novel potential and promising therapeutic targets for the future treatment of this condition.

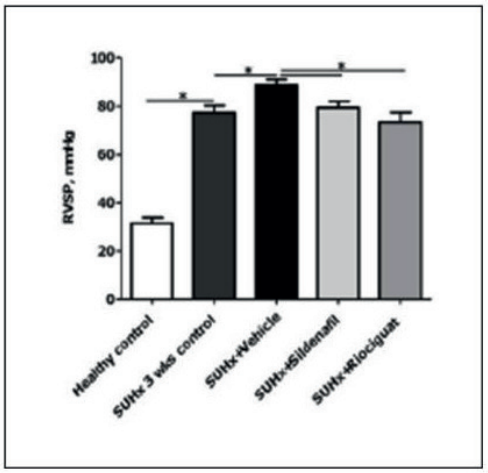
Cation influx in MLEC from WT and TRPC6-/- mice. Increase in the [Ca2+]i upon ischaemia-reperfusion. WT – wild type; MLEC - murine lung endothelial cells. b) Post-ischaemic vascular leakage in isolated lungs of WT and TRPC6-/- mice. Kfc - capillary filtration coefficient. c) Proposed signal transduction cascade in LIRE. Pharmacological interventions are indicated in red (Nat Commun. 2012;3:649). (DAG - diacylglycerol; Ex - extracellular; In - intracellular; OAG - Oleoylacetylglycerol; PA - phosphatidic acid; PIP2 – phosphatidylinositol-4,5-bisphosphate. LIRE – lung ischaemia-reperfusion-induced oedema.)

Research Highlight #3:

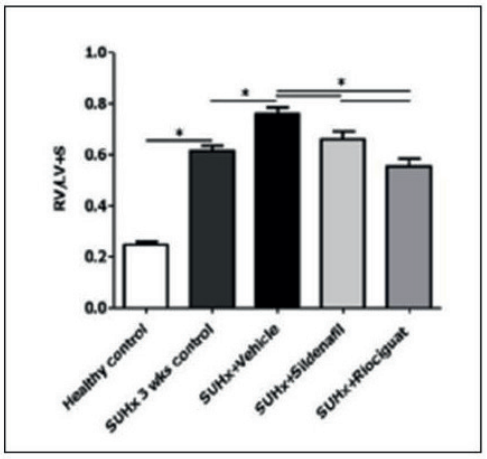
It has been previously described that the nitric oxide (NO)-soluble guanylate cyclase (sGC)-cyclic guanosine monophosphate (cGMP) signaling cascade is impaired in pulmonary arterial hypertension (PAH). This study aimed to investigate the role of NO-sGC-cGMP signaling pathway and effects of sGC stimulation by riociguat in experimental model of severe PAH, such as exposure of the rats to the vascular endothelial growth factor receptor antagonist SU5416 and hypoxia (SUHx). Results demonstrated that riociguat successfully reduced right ventricular systolic pressure and right ventricular hypertrophy and improved right heart function, in comparison with placebo administration. Additionally, riociguat had beneficial effects on pulmonary vascular remodeling, as evident from significantly decreased proportion of occluded arteries and attenuated neointima/media ratio, compared to placebo. Finally, the study revealed that riociguat had greater beneficial therapeutic effects on hemodynamics and right ventricular hypertrophy than sildenafil. Therefore, riociguat may represent a promising treatment option for PAH patients.

a) Effects of riociguat on hemodynamics in SUHx rats. RVSP – right ventricular systolic pressure; SUHx – SU5416 and hypoxia. b) Effects of riociguat on right ventricular hypertrophy in SUHx rats. RV/(LV+S) – right ventricle/(left ventricle plus septum). c) and d) Effects of riociguat on pulmonary vascular remodeling in SUHx rats. (PLoS One. 2012;7(8):e43433)

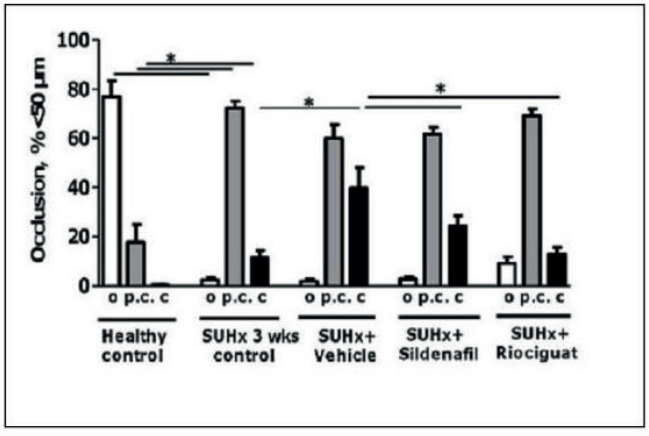
a)



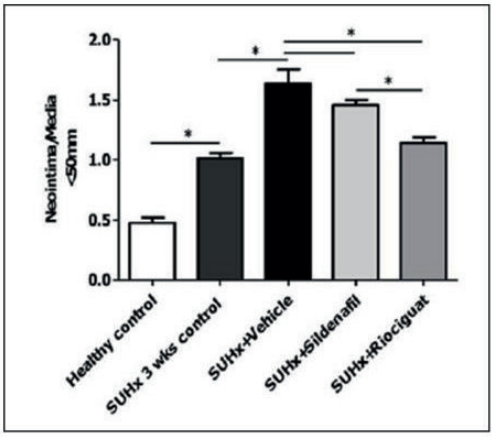
b)



c)

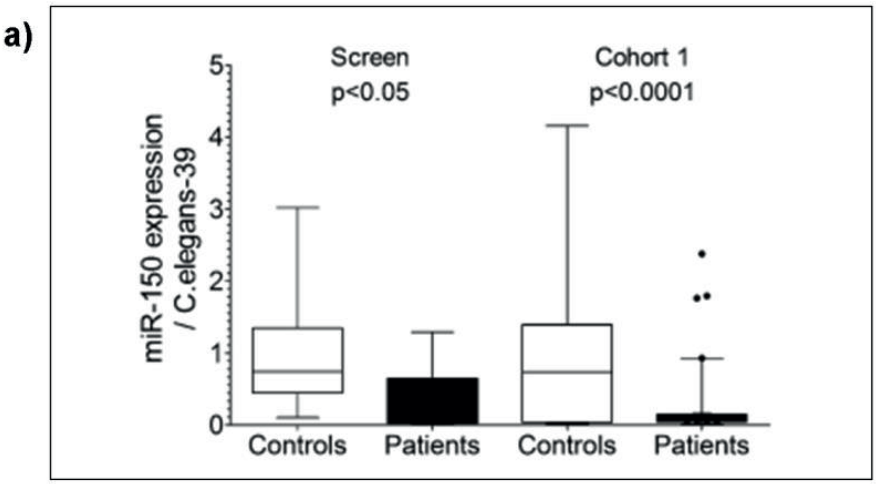


d)

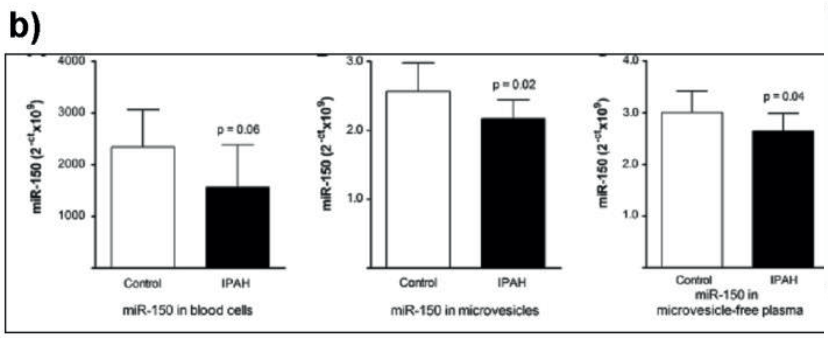


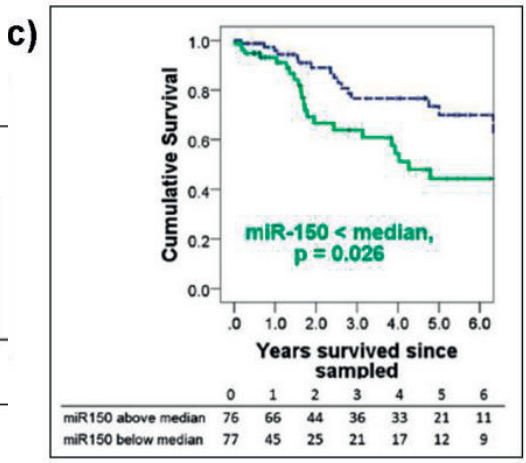
Research Highlight #4:

In the recent years it has become clear that a variety of microRNAs (miRs) are altered, and therefore may be potentially implicated in the pathology of pulmonary arterial hypertension (PAH). This study aimed to investigate whether a particular miRNA, miR-150 was dysregulated in patients with PAH in comparison with healthy controls, and furthermore, if it could be linked to the severity of the disease. Results from the study demonstrated decreased circulating levels of miR-150 in patients suffering from PAH, compared to healthy controls. Importantly, reduced levels of miR-150 were associated with poor survival of the patients with PAH. Finally, miR-150 levels were also significantly decreased in circulating microvesicles; therefore, our data suggest that miR-150 may represent a promising new prognostic biomarker for this life-threatening and severe pulmonary vascular disease.



a) MicroRNA-150 (miR-150) levels in patients with pulmonary arterial hypertension (PAH). b) Distribution of miR-150 expression in blood cells, microvesicles and microvesicles-free plasma of controls and patients with idiopathic pulmonary arterial hypertension (IPAH). c) Kaplan–Meier analysis of survival, stratified by median miR-150 cutoff. Survival among patients with PAH with normalized miR-150 levels above the median is indicated by the blue dashed line and in patients with levels below the median by the green solid line. Table indicates numbers at risk over time in years. (Reprinted with permission of the American Thoracic Society. Copyright © 2013 American Thoracic Society. Rhodes et al., 2013. Reduced microRNA-150 is associated with poor survival in pulmonary arterial hypertension. 187:294-302. Official Journal of the American Thoracic Society.)





Number of papers published by DZL Faculty in 2012 - Disease Area Pulmonary Hypertension: 36

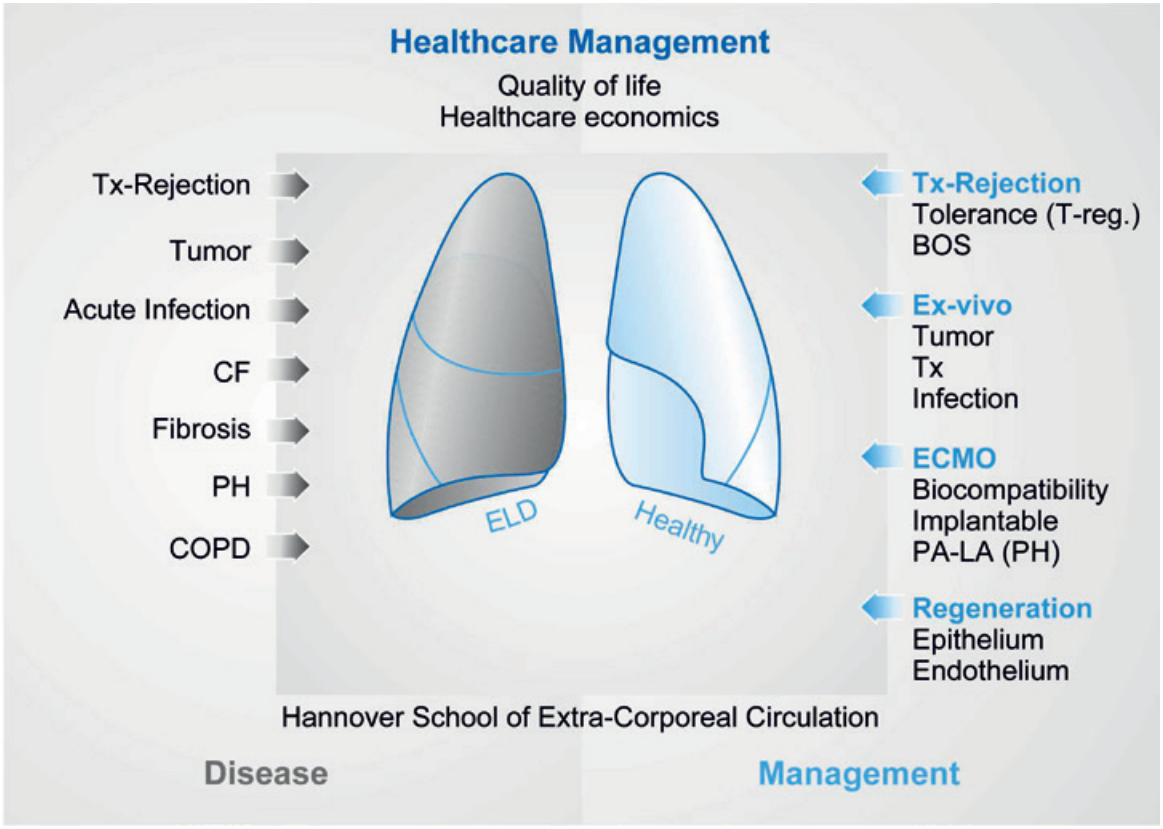
Highlighted Publications

1. Hoeper MM, Huscher D, Ghofrani HA, Delcroix M, Distler O, Schweiger C, Grunig E, Staehler G, Rosenkranz S, Halank M, Held M, Grohé C, Lange TJ, Behr J, Klose H, Wilkens H, Filusch A, Germann M, Ewert R, Seyfarth HJ, Olsson KM, Opitz CF, Gaine SP, Vizza CD, Vonk-Noordegraaf A, Kaemmerer H, Gibbs JS, Pittrow D. Elderly patients diagnosed with idiopathic pulmonary arterial hypertension: Results from the COMPERA registry. Int J Cardiol. 2012. S0167-5273(12)01401-5.
2. Pullamsetti SS, Doebele C, Fischer A, Savai R, Kojonazarov B, Dahal BK, Ghofrani HA, Weissmann N, Grimminger F, Bonauer A, Seeger W, Zeiher AM, Dimmeler S, Schermuly RT. Inhibition of microRNA-17 improves lung and heart function in experimental pulmonary hypertension. Am J Respir Crit Care Med. 2012;185(4):409-19.
3. Weissmann N, Sydykov A, Kalwa H, Storch U, Fuchs B, Mederos y Schnitzler M, Brandes RP, Grimminger F, Meissner M, Freichel M, Offermanns S, Veit F, Pak O, Krause KH, Schermuly RT, Brewer AC, Schmidt HH, Seeger W, Shah AM, Gudermann T, Ghofrani HA, Dietrich A. Activation of TRPC6 channels is essential for lung ischaemia-reperfusion induced oedema in mice. Nat Commun. 2012;3:649.
4. Savai R, Pullamsetti SS, Kolbe J, Bieniek E, Voswinckel R, Fink L, Scheed A, Ritter C, Dahal BK, Vater A, Klussmann S, Ghofrani HA, Weissmann N, Klepetko W, Banat GA, Seeger W, Grimminger F, Schermuly RT. Immune and inflammatory cell involvement in the pathology of idiopathic pulmonary arterial hypertension. Am J Respir Crit Care Med. 2012;186(9):897-908.
5. Kwapiszewska G, Markart P, Dahal BK, Kojonazarov B, Marsh LM, Schermuly RT, Taube C, Meinhardt A, Ghofrani HA, Steinhoff M, Seeger W, Preissner KT, Olschewski A, Weissmann N, Wygrecka M. PAR-2 inhibition reverses experimental pulmonary hypertension. Circ Res. 2012; 110(9):1179-91.

End-Stage Lung Disease

Disease Area Leaders	Prof. Dr. Dr. Axel Haverich (BREATH) Prof. Dr. Robert Voswinckel (UGMLC)
Participating DZL Partner Sites	BREATH, UGMLC, CPC-M
Number of Participating DZL Faculty	22

Various acute and chronic lung disorders ultimately lead to end-stage lung disease (ELD). If all options of mechanical ventilation have been exhausted, death is imminent, but two treatment modalities remain: extracorporeal lung oxygenation (ECMO) and lung transplantation (LTx). Today, ECMO therapy remains restricted to short-term application, primarily as bridge to transplantation and as bridge to recovery in acute pulmonary infectious disease (for example, H1N1). In chronic injury, LTx remains the only available therapy with the potential of true long-term survival. LTx, however, is limited to highly selected patients, excludes any pulmonary malignancy, and long-term survival is severely compromised by chronic rejection. Regenerative therapies that promote endogenous repair, cell transplantation, or tissue engineering are not available. The DZL ELD program aims to refine transplantation procedures to minimize acute and chronic rejection, optimize ECMO therapy towards fully implantable devices, and set the stage for regeneration of diseased lung tissue.



The Thematic Priority Area "End-stage Lung Diseases" focuses on acute and chronic end-stage pulmonary diseases not responding to conventional therapy. The number of patients with terminal pulmonary disease is increasing. This is true for both acute pulmonary injury from ARDS and infection, chronic disease, pulmonary hypertension, fibrosis, COPD and cystic fibrosis, as well as malignancies. At the DZL, end-stage lung disease is being tackled with a multi-faceted approach by stem-cell researchers, bioengineers, and first-line clinicians and surgeons. Lung transplantation, which is often the only option for patients with end-stage lung disease, requires intensive patient care, both before and after transplantion, and shapes and drives the urgent need for research in this area.

Goals Followed in 2012 – End-Stage Lung Disease

Goal 1 – Lung Transplantation

- Immunology in Lung Transplantation
  - Immunophenotyping of clinical lung transplant recipients before and after lung transplantation (LTx)
    - Creation of SOPs for FACS of Treg, MDSC and allo-Ab for use at participating locations
    - Monitoring of a regulatory T cell phenotype in PBMC and BAL after LTx
- Immunological tolerance
  - Evaluation of alternative methods for cytoreduction in a porcine lung transplantation model
  - Optimization of alloantigen application in a porcine lung transplantation model
  - Investigation of the mechanism of T cell regulation in a porcine lung transplant model
- Bronchiolitis Obliterans
  - New therapeutic strategies for the treatment of neutrophilic inflammation in chronic graft dysfunction after lung transplantation
    - Identification of risk factors and disease-defining variables
    - Development of a flow chart with follow-ups in the LTx cohort
    - Build a database and identify affected patients
    - Follow-up and identification of a cohort (50 min) of LTx candidates with neutrophilic graft dysfunction
    - Identification of new therapeutic strategies in clinical pilot studies
  - Mechanism of bronchiolitis obliterans syndrome
    - Identification of candidate molecules in the murine model of Lutx-BOS

Goal 2 – ECMO

- ECMO and artificial lung - experimental research
  - Development of biocompatible gas exchange membranes
  - Identification of effective strategies to prevent biofilm formation in the system
- Clinical program (lung failure of various origins)

- Development of a computer-based simulation program for ECMO optimization
- ECLS in patients with pulmonary hypertension and right heart failure
  - Development of a clinical trial protocol (comparison of veno-arterial ECMO versus central ILA in PH patients with right heart failure)

Goal 3 – Regeneration

- iPS ECs for biohybrid ECMO and PH
  - Establishment of endothelial differentiation of iPS cells and characterization of iPS-derived ECs
  - iPS generation from transgenic reporter lines for monitoring of endothelial differentiation and genetic enhancement
  - Optimization of endothelial differentiation and enrichment of the generated iPS ECs
  - Establishment of protocols for the production of iPS with microvascular EC phenotype
- Therapy of lung diseases based on pluripotent stem cells
  - Establishment of respiratory differentiation of human iPS cells and characterization of these cells
  - Human iPS generation of transgenic reporter lines for monitoring the respiratory differentiation and genetic enhancement

Goal 4 – Ex Vivo Lung Perfusion

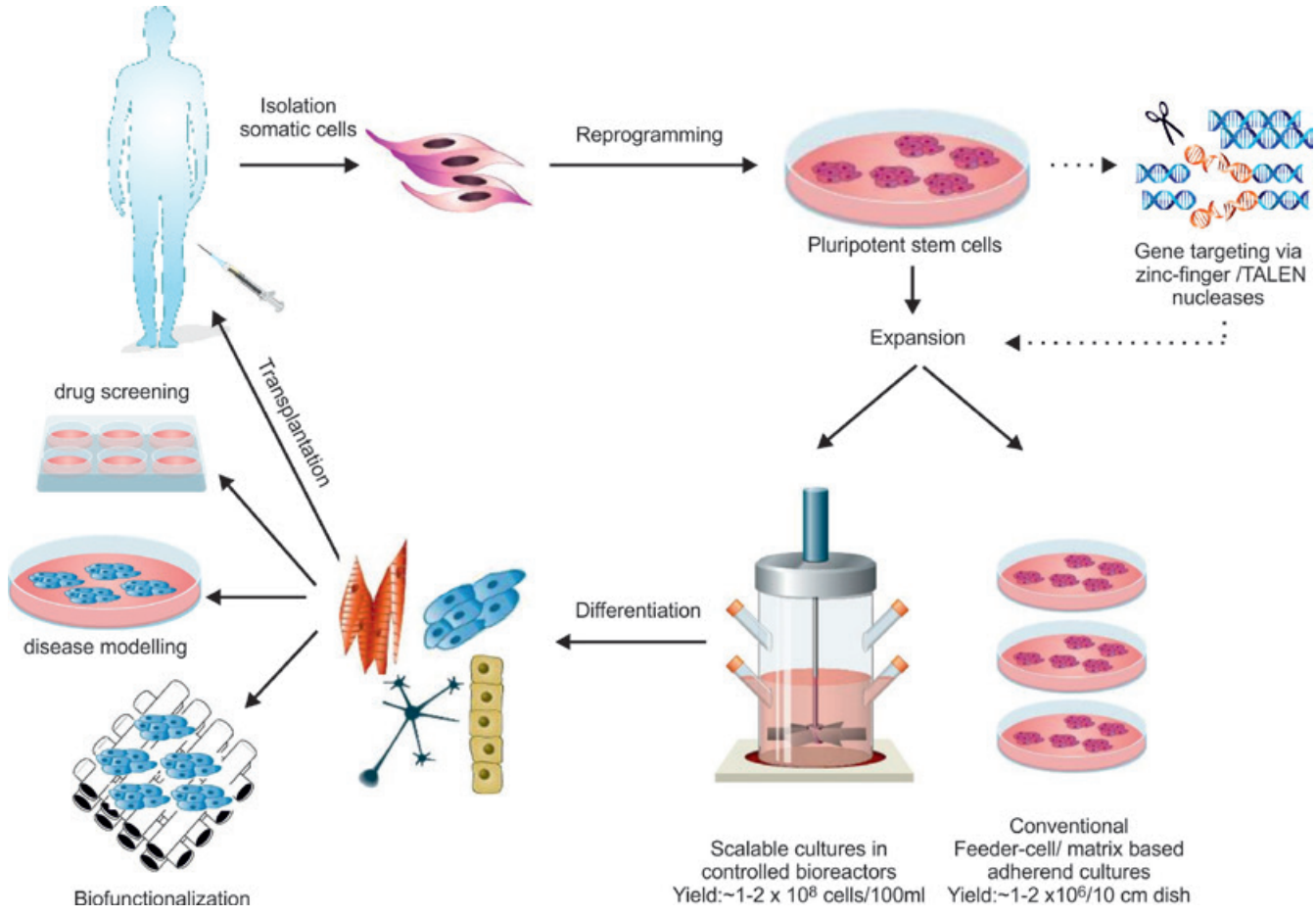
- Use of an innovative ex vivo lung perfusion (OCS) system for the treatment of terminal malignant lung diseases
  - Miniaturization of the system for use in small animals (mouse, rat)
  - Establishment of a tumor model in large animals

Goal 5 - Healthcare Management

- Analysis of the supply situation of patients with terminal lung disease (ELD) and patients after lung transplantation
  - Systematic literature search on project-specific survey instruments
  - Data protection concept, apply for ethics commission
  - Software selection, programming and interface adaptation

2012 Research Highlights – End-Stage Lung Disease

Research Highlight #1:



Schematic representation of human induced pluripotent stem cell (iPSC) generation cells including genetic modification and expansion. Methods are being established for mass expansion of human iPSC in controllable stirred bioreactors with the aim of scalable vascular differentiation. Reprogramming protocols are being developed and refined, along with reporter lines to monitor the differentiation of stem cells into respiratory tissues. In addition to direct transplantation, the colonization of artificial surfaces with these cells is planned, with the ultimate aim of regeneration of diseased lung tissue.

Research Highlight #2:

45-year-old patient with terminal lung injury and ARDS in "awake" ECMO. This method has been pioneered and used more than 50 times at the DZL Partner Site, the Medical School of Hannover as a "bridge to transplant"/ "bridge to recovery". Awake ECMO has advantages over conventional mechanical ventilation including reduced risk of ventilator-associated pneumonia, a leading cause of death in end-stage lung disease patients. The fact that patients are awake and breathe spontaneously is also an advantage as active physiotherapy is feasible and patients can be better conditioned prior to transplantation. (Am J Respir Crit Care Med. 2012;185:763-8.)

Number of papers published by DZL Faculty in 2012 - Disease Area End-stage Lung Disease: 27

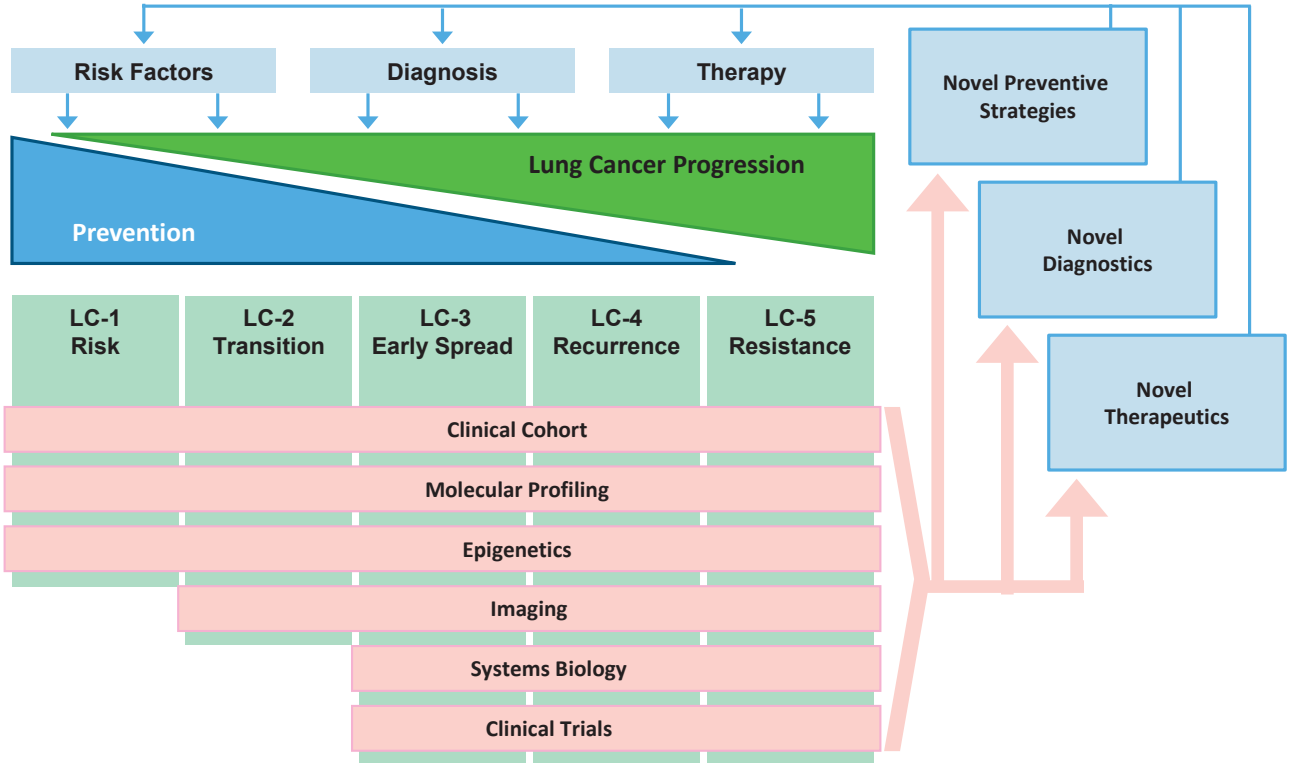
Highlighted Publications

1. Fuehner T, Kuehn C, Hadem J, Wiesner O, Gottlieb J, Tudorache I, Olsson KM, Greer M, Sommer W, Welte T, Haverich A, Hoeper MM, Warnecke, G. Extracorporeal membrane oxygenation in awake patients as bridge to lung transplantation. American Journal of Respiratory and Critical Care Medicine 2012; 185 (7), pp. 763-768.
2. Ius F, Kuehn C, Tudorache I, Sommer W, Avsar M, Boethig D, Fuehner T, Gottlieb J, Hoeper M, Haverich A, Warnecke G. Lung transplantation on cardiopulmonary support: Venoarterial extracorporeal membrane oxygenation outperformed cardiopulmonary bypass. Journal of Thoracic and Cardiovascular Surgery 2012; 144 (6), pp. 1510-1516.
3. Olmer, R., Lange, A., Selzer, S., Kasper, C., Haverich, A., Martin, U., Zweigerdt, R., Suspension culture of human pluripotent stem cells in controlled, stirred bioreactors. Tissue Eng Part C: Methods, (2012) Volume 18, Issue 10, pp. 772-784.
4. Suhling H, Dettmer S, Rademacher J, Mark G, Shin H-O, Tudorache I, Kühn C, Haverich A, Welte T, Warnecke G, Gottlieb J. Spirometric obstructive lung function pattern early after lung transplantation. Transplantation 2012; 93 (2), pp. 230-235.
5. Warnecke G, Moradiellos J, Tudorache I, Kühn C, Avsar M, Wiegmann B, Sommer W, Ius F, Kunze C, Gottlieb J, Varela A, Haverich A, Normothermic perfusion of donor lungs for, reservation and assessment with the Organ Care System Lung before bilateral transplantation: A pilot study of 12 patients. The Lancet 2012; 380 (9856), pp. 1851-1858.
6. Wiesner O, Hadem J, Sommer W, Kühn C, Welte T, Hoeper MM, Extracorporeal membrane oxygenation in a nonintubated patient with acute respiratory distress syndrome. European Respiratory Journal 2012; 40 (5), pp. 1296-1298.

Lung Cancer

Disease Area Leaders	Prof. Ursula Klingmüller (TLRC) Prof. Michael Thomas (TLRC)
Participating DZL Partner Sites	ARCN, BREATH, TLRC, CPC-M
Number of Participating DZL Faculty	30

Lung cancer is a high incidence, high mortality disease, with non-small cell lung cancer (NSCLC) prevailing. At diagnosis, 20-30 % of patients present with small cell lung carcinoma (SCLC) bearing a particularly poor prognosis, and almost 40 % of NSCLC-patients present with metastases. To tackle this problem, chemotherapy is combined with locoregional treatment such as surgery and radiotherapy. The selection of patients for these treatments does not consider biological properties driving the propagation and spread of the disease; hence the outcome is very variable. Thus, the identification of relevant molecular features is urgently needed to advance matching of selected treatments to patients. Lung cancer research in the DZL is an integrative in-depth program exploiting clinically well characterized sample sets with epidemiologic, genetic, epigenetic and systems biology approaches, and has the ultimate goal of developing personalized therapies to improve patient outcomes.



Goals Followed in 2012 – Lung Cancer

Goal 1 – Epigenetic Markers for Lung Cancer Risk Prediction and Early Detection

- Changes in methylation patterns
  - Optimization of methods for epigenetic analysis
- Clinical validation of epigenetic cancer markers
  - Review of the predictive power of epigenetic markers

Goal 2 – Determinants of Somatic Progression From Airway Epithelium to Lung Cancer

- Carcinogenic stimuli in the lung tissue model
  - Validation of candidate genes using tissue microarray technology (TMA)
- Comparative analysis of DNA methylation profiles
  - Identification of differential methylation profiles in the transition of COPD to lung cancer
  - Biomaterial analysis with probes from fully characterized individuals from a patient cohort
- Clinical validation of transition-defining markers
  - Validation of markers from early screening programs
  - Identification of epigenetic risk factors

Goal 3 – Mechanisms of Early Spread and Predicting Strategies for Intervention

- Dynamics of signal transduction and cell migration in lung cancer cells
  - Quantitative analysis of the TGFbeta, IGF and EGF-induced signal transduction pathways and creation of individual pathway models
  - Analysis of signal transduction at the single cell level and integration into multi-scale model
- Molecular models for improved prognosis
  - Trend analysis determining patterns
  - Validation determining prognosis pattern
  - Building a patient cohort

Goal 4 – Response and Recurrence in the Combination of Systemic and Radiation Therapy

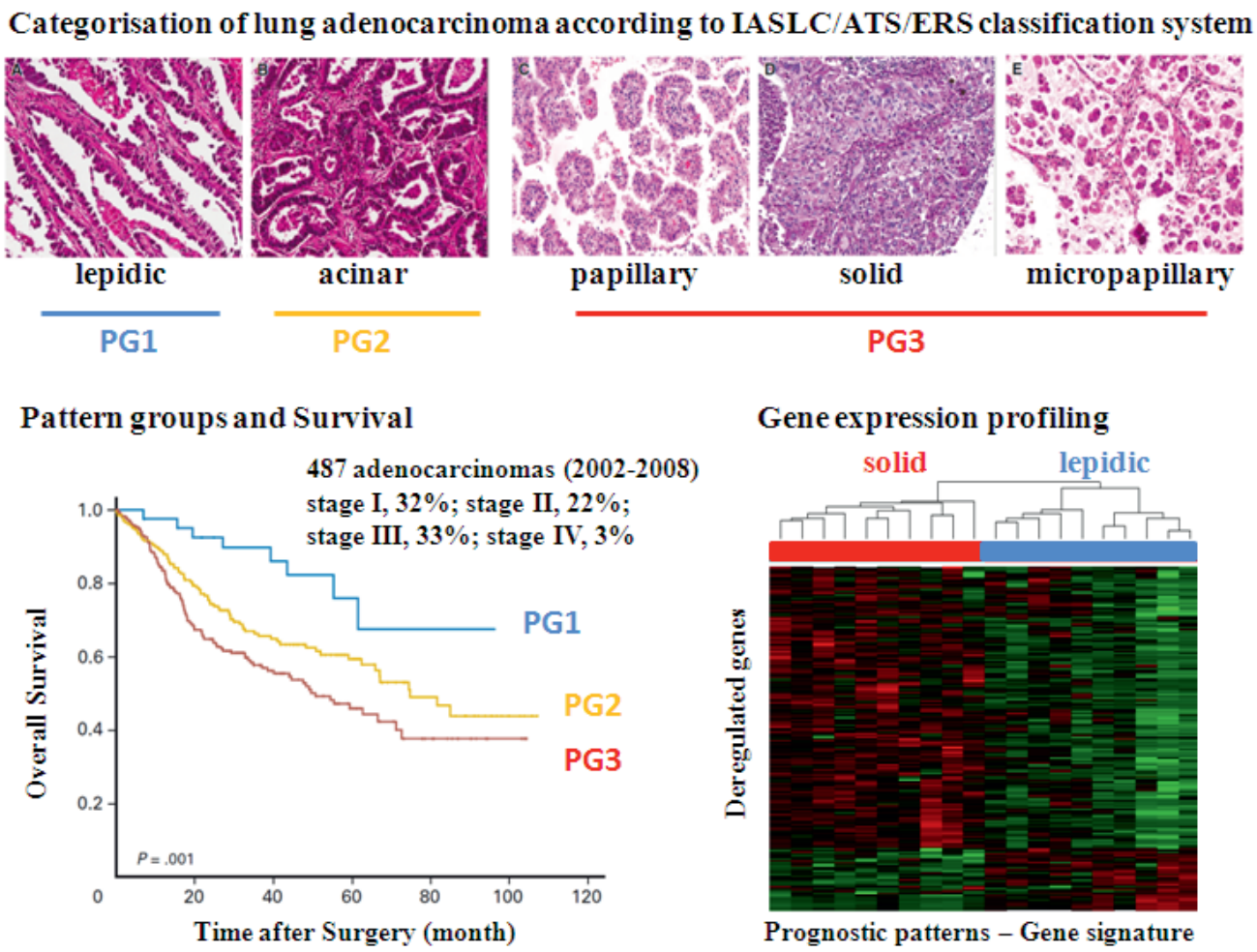
- Molecular mechanisms of therapy resistance
  - Establishment of integrative dynamic models of repair mechanisms and signal transduction of growth factors
- Characterization of the response to systemic and radiation therapy
  - Analysis of tumor response by morphological and functional imaging
  - Building a patient cohort
- Improved treatment options
  - Development of decision options
  - Identification of targets for maintenance therapy

Goal 5 – Strategies to Mitigate Therapy Resistance

- EGF Receptor signal transduction and resistance mechanisms in preclinical models
  - Identification of resistance mechanisms of EGF receptor signal transduction
  - Development of strategies to overcome resistance based on mathematical models
- Sequential biomaterial collection in metastatic disease
  - Optimization of biomaterial collection, processing, and tissue banking
  - Building a patient cohort
- Therapy resistance
  - Inspection of molecular targeted therapies in Phase I / II studies with renewed biomaterial acquisition
  - Improving the identification of resistance mechanisms of not yet clinically tested substances

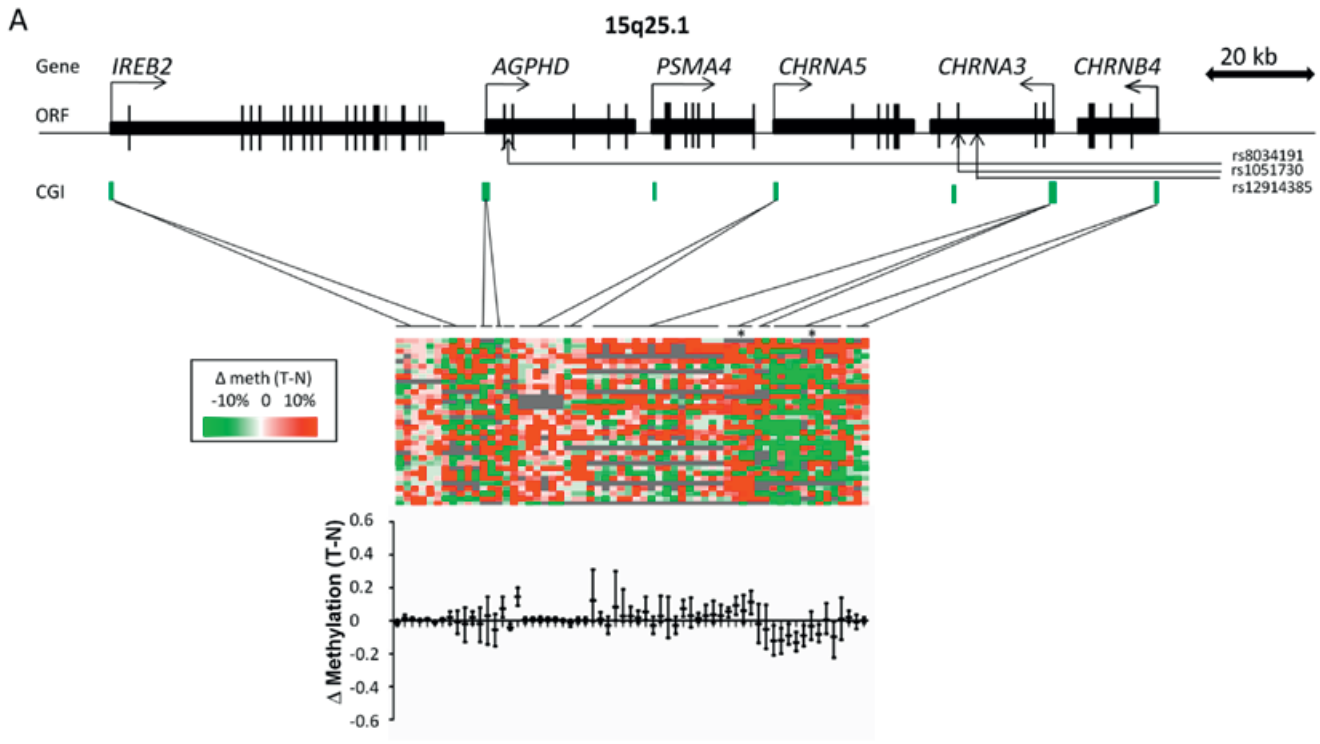
2012 Research Highlights – Lung Cancer

Research Highlight #1:



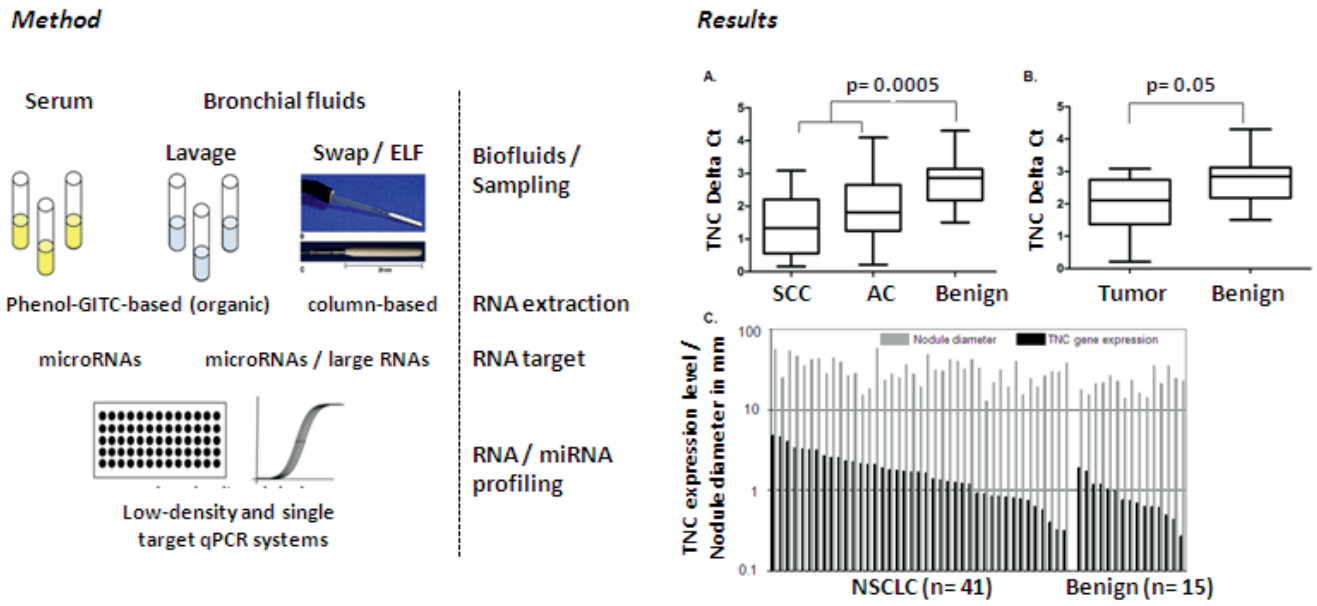
Utilizing the extensive DZL biobanking capabilities we were able to demonstrate the strong prognostic impact of adenocarcinoma subtypes as defined by the ATS/ERS-classification (PG, Prognostic Group) (J Clin Oncol 2012; 30: 1438-46). Histological patterns could be assigned to specific gene signatures as outlined for the lepidic and solid type. In the solid type - with a substantially worse prognosis - upregulated genes were linked to pathways representing anti-apoptosis, cell cycle progression and MAPK- and NFkB-signalling. In a next step, the new hypotheses developed from the results of these screening studies will be investigated in preclinical models.

Research Highlight #2:



Genome-wide association studies have highlighted three major lung cancer susceptibility regions at 15q25.1, 5p15.33 and 6p21.33. To gain insight into the possible mechanistic relevance of the genes in these regions, we investigated the regulation of candidate susceptibility gene expression by epigenetic alterations in healthy and lung tumor tissues. Tumor hypomethylation in the promoter region of CHRNB4 was frequent, with a median difference of 8% ($P<0.001$), which resulted in overexpression of the transcript in tumors ($P<0.001$). The results suggest epigenetic deregulation of nicotinic acetylcholine receptor subunit (nAChR) genes, which in the case of CHRNB4, is strongly associated with genetic lung cancer susceptibility variants and a functional impact on tumorigenic potential (Oncogene. 2013;32: 3329-38.). Current efforts are focused on epigenetic screening in blood to identify epigenetic risk factors.

Research Highlight #3:



We investigated whether biomarker analysis in endobronchial epithelial-lining fluid (ELF) collected by bronchoscopic microsampling (BMS) and other specimens may be useful for a definitive preoperative diagnosis. ELF was collected from clinically relevant lung cancer patients by bronchoscopic microsampling close to the indeterminate pulmonary nodule and the contralateral site. Gene expression profiling resulted in potential biomarkers upregulated in ELF of cancer patients. Here, tenascin-C was validated in an independent cohort of 56 patients to be associated with malignant pulmonary nodules. Combined analysis of tenascin-C expression and the nodule size improved the prediction of malignancy (AUC= 0.84, p= 0.0001) in this patient cohort. Our study suggests that the analysis of specific biomarkers in ELF collected by BMS could be a potentially useful adjunct to other diagnostic techniques (Kahn et al., Early detection of lung cancer by molecular markers in endobronchial epithelial-lining fluid. J Thorac Oncol. 2012; 7(6):1001-8.)

Number of papers published by DZL Faculty in 2012 - Disease Area Lung Cancer: 60

Highlighted Publications

1. Scherf DB, Sarkisyan N, Jacobsson H, Claus R, Bermejo JL, Peil B, Gu L, Muley T, Meister M, Dienemann H, Plass C, Risch A. Epigenetic screen identifies genotype-specific promoter DNA methylation and oncogenic potential of CHRNB4. Oncogene. 2013 Jul 11;32(28):3329-38. epub 2012 Sep 3
2. Peifer M et al . Integrative genome analyses identify key somatic driver mutations of small-cell lung cancer. Nat Genet 2012;44:1104-1110.
3. Tian F, Mysliwietz J, Ellwart J, Gamarra F, Huber RM, Bergner A. Effects of the Hedgehog pathway inhibitor GDC-0449 on lung cancer cell lines are mediated by side populations. Clin Exp Med 2012;12:25-30.
4. Warth A, Muley T, Meister M, Stenzinger A, Thomas M, Schirmacher P, Schnabel PA, Budczies J, Hoffmann H, Weichert W. The novel histologic International Association for the Study of Lung Cancer/American Thoracic Society/ European Respiratory Society classification system of lung adenocarcinoma is a stage-independent predictor of survival. J Clin Oncol 2012;30:1438-1446.
5. Kahn N, Meister M, Eberhardt R, Muley T, Schnabel PA, Bender C, Johannes M, Keitel D, Sültmann H, Herth FJ, Kuner R. Early detection of lung cancer by molecular markers in endobronchial epithelial-lining fluid. J Thorac Oncol. 2012;7:1001-8.
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Research Infrastructure

Central to the success of a concerted translational strategy is access to state of the art research infrastructure which crosses all disease areas. To support and facilitate its translational research efforts, the DZL invests in platform technologies to which all DZL researchers have access. Integrated Data Management, Biobanking, and Imaging resources are supported by DZL funds. Furthermore, DZL researchers have access to some of the largest lung disease patient and biomaterial cohorts in the world. For example, CAPNETZ – Network of Excellence Community Acquired Pneumonia, is now integrated into the DZL. CAPNETZ connects clinical, microbiological and basic research in order to gain knowledge of the pathogenesis of community acquired pneumonia (CAP) and is the most comprehensive CAP database in the world.

Taskforce Data Management

The integration of data across research sites and platforms remains a key challenge. In 2012 a Data Management taskforce was established at the DZL. This task force has the mandate to develop an integrated, streamlined solution that can handle vast amounts of data from diverse sources and formats. Currently two different software solutions are under evaluation and a pilot project has been initiated using data from the Disease Area Lung Cancer.

Platform Biobanking

Scientific Coordinators	Prof. Dr. Andreas Günther (UGMLC) Dr. Thomas Muley (TLRC)
Participating DZL Partner Sites	ARCN, BREATH, UGMLC, TLRC, CPC-M
Number of Participating DZL Faculty	11

Introduction and Aims:

Biomaterials are a key component in translational lung research. Translational research projects can either be undertaken following a "bottom up" (from the test tube to humans) or a "top down" approach (from humans to a cellular mechanism). In both cases, biomaterials are of utmost importance, as they are the basis for the development of new pathomechanistic concepts, innovative therapies and individualized treatment options ("individualized medicine", "targeted therapy"), the identification of prognostically relevant biomarkers, and for the verification of basic science findings.

Goals followed in 2012 – Platform Biobanking

Goal 1 – Build a DZL Biobank Portal

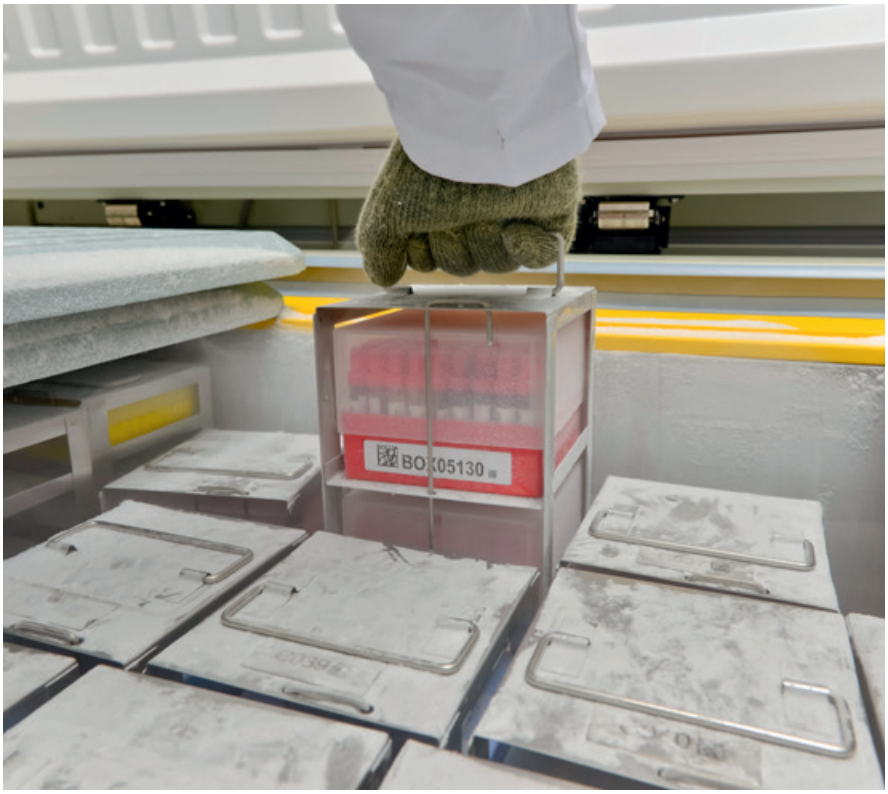
- Formation and coordination of working groups
- Establishment of regular meetings
- Establishment of DZL Biobank portal

Goal 2 – Harmonization of Procedures and Guidelines

- Definition of "DZL biobanking working group" and conduct regular meetings
- Identification of existing SOPs

Goal 3 - Harmonization of Phenotyping Tools

- Identification of existing phenotyping tools
- Creation of a centralized, disease independent parameter catalog of bio-material collection, storage and documentation



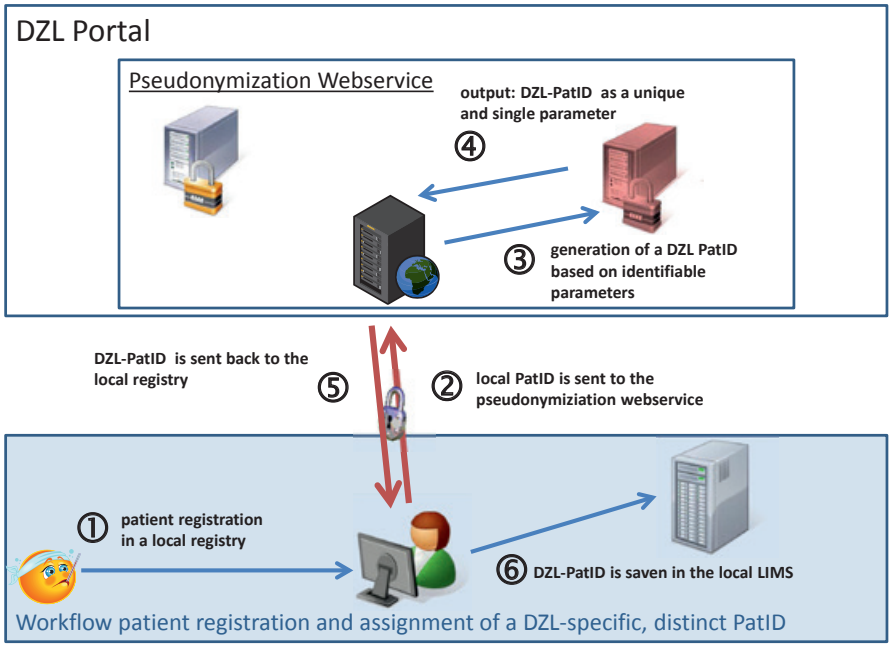


Figure 1

The centrally-organized DZL-platform "Biobanking" aims to provide easy and direct access to DZL members as well as external partners to biomaterials from patients with the pulmonary diseases studied within the DZL. In order to reach these goals the following achievements have been accomplished:

1. The structure, organization, informed consent procedures, data management and quality control procedures and biomaterial collections of site-specific, local biobanks has been assessed.

2. The data obtained in 1) have been transferred into the "biobanking" website of the DZL-Homepage (www.dzl.de). Every scientist can now inform her/himself as to the availability of collected biomaterials for a given disease entity and which formal aspects are needed to be fulfilled in order to gain access to these biomaterials.

3. In order to be able to collect biomaterials within the DZL under a harmonized informed consent procedure, the platform members have developed a broad consent form that is based on more recently established larger biobanks (e.g. IBDW; Interdisziplinäre Biomaterial- und Datenbank Würzburg or m4 biobank alliance Munich), as well as on a most recent version of a broad consent form developed by the "Arbeitsgruppe Biobanken im Arbeitskreis medizinischer Ethikkommissionen

(AK-EK)" which will be the underlying basis for future biobank-based informed consent procedures throughout Germany. This DZL informed consent procedure, alongside with a DZL-wide data protection concept, will be submitted to the first ethics committee in 2013 and used as the standard informed consent procedure for all further biomaterial collections. The DZL informed consent procedure not only covers the collection and the timely unlimited use of biomaterials but also the acquisition and storage of phenotyping data including radiographic and histological data and the acquisition, storage and use of genetic data including next generation sequencing (deep sequencing). The informed consent form also covers broad consent for children and legal guardians. It will allow easy forwarding and exchange of any data among DZL scientists according the data protection concept.

4. The data safety concept, which is based on most recent standards (TMF, data safety protection officers), makes use of a double pseudonymization process, making re-identification of patients impossible (see figure 1). Based on this technique, the generation of site, specimen and date-of-collection-specific LabIDs is possible throughout all DZL sites, allowing the generation of a unique and definite, DZL-wide Lab-ID. The software and hardware structure necessary to provide this service is already implemented. The votes of the TMF and local data protection officers are currently pending. As soon as these and the ethic votes have been obtained, the entire structure of the DZL covering biomaterial acquisition, collection of phenotyping data and data analysis by means of a data warehouse concept will be available.

5. In order to improve the quality of the collected data and biomaterials, the platform biobanking has been systematically reviewing all procedures associated with patient identification, biomaterial withdrawal, primary processing for the various purposes (RNA, protein-isolation, cell isolation, etc), shipment and secondary steps necessary for definite analysis. A complete list of procedures has been established and serves as underlying basis for the development of DZL-wide SOPs, which will result in a harmonization of the currently SOPs available at different DZL sites. A uniform template has been developed and the first harmonized SOPs are currently circulating among the Disease Area members for final approval.

6. As biomaterials are stored locally, the platform members agreed to use their individual storage and labeling systems. Most DZL members use 2D-barcode tubes from different suppliers and different laboratory information and management systems (LIMS) for sample registration and tracking. As outlined above samples collected under a harmonized DZL informed consent will be additionally labeled with a central DZL-unique sample ID (figure 2).

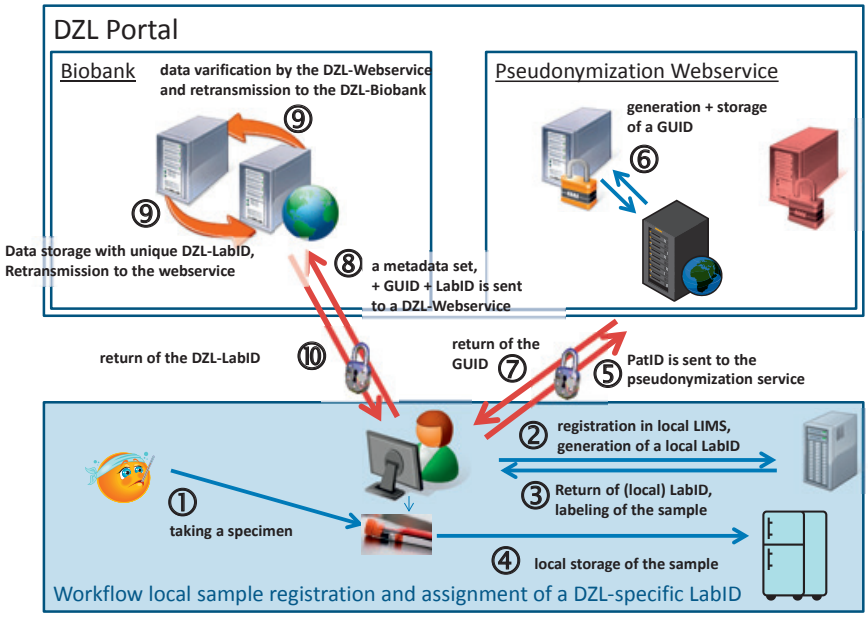


Figure 2

Phenotyping data will be either collected in the frame of DZL-associated registries (e.g. COSYCONET, eurIP-Fnet) or phenotyping tools, or by using special tools to be developed for the DZL. In any case the double pseudonymization process will allow samples to be linked with phenotyping data (biometric data, family history, occupational history and disease-specific clinical parameters). To further faciliate this process and to be able to integrate data from several DZL resources and to also include research data as reasonable (e.g. all ~ omics datasets), an overarching data warehouse system was developed, which is based on i2b2 (Informatics for Integrating Biology & the Bedside). The proposed IT-structure and IT management concept will be established according to figure 3.

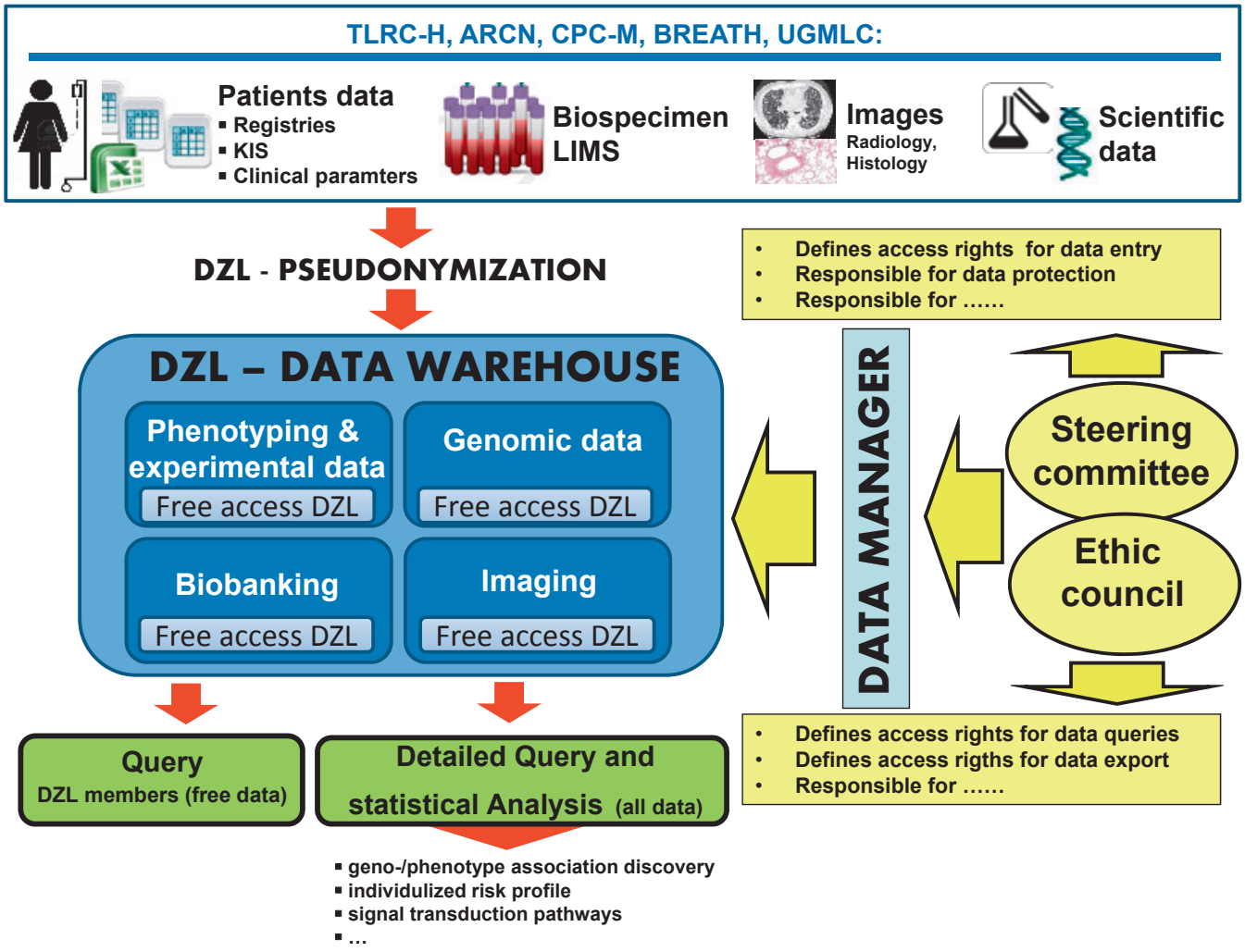


Figure 3

Platform Imaging

Scientific Coordinators	Prof. Dr. med. Hans-Ulrich Kauczor, TLRC Prof. Dr. med. Matthias Ochs, BREATH Prof. Dr. Heinz Fehrenbach, ARCN
Participating DZL Partner Sites	ARCN, BREATH, UGMLC, TLRC, CPC-M
Number of Participating DZL Faculty	18

Overview

A wide range of imaging approaches is used in the life sciences to understand living systems and to support the drug discovery processes. The platform 'Imaging' has been established as a network of complementing expertise and infrastructure within the DZL to ensure scientific exchange and access to cutting-edge imaging technologies in research. Comprising radiology and microscopy, the platform 'Imaging' aims to identify and benefit from the interfaces between them. The core function of the Platform is to offer, disseminate and share imaging technology.

In 2012 the structure of the platform management was developed and established. In order to improve the communication among all members of the platform and to coordinate the conduct of projects across partner sites, a central coordination office managed by the Translational Lung Research Centre (TLRC) has been established in Heidelberg. Also supported by the TLRC, an IT specialist started his work in 2012 and laid the foundation for the central imaging database (Image Bank), the core project of the Platform Imaging.

The Image Bank will comply with the ethical and legal framework, data protections rules and the corresponding body of rules and regulations in operation at the partner sites within the DZL.

Goals followed in 2012 – Platform Imaging

Goal 1 - Framework
- Establishment of a central coordinating office in Heidelberg

Goal 2 - Exchange of Methodologies
- Implementation of first exchanges
- Meeting in Hannover to discuss use of imaging in disease areas ALI, COPD, and ELD

Goal 3- Basic Rules
- By-laws
- Definition of the most important imaging procedures requiring standard protocols (SOPs)
- First protocols agreed upon
- Compilation of cost

Goal 4 – Image Bank
- Development of a concept for the Image Bank
- Identification of basic variables
- Specifications for the Database server
- Definition of location/ in Heidelberg at the dkfz
- Acquisition

Core project of the Platform Imaging: The Image Bank

Idea

- Centralised Database
- Accessible from all sites
- Query-Retrieve System
- User Managament
- Local Storage for Imaging Data

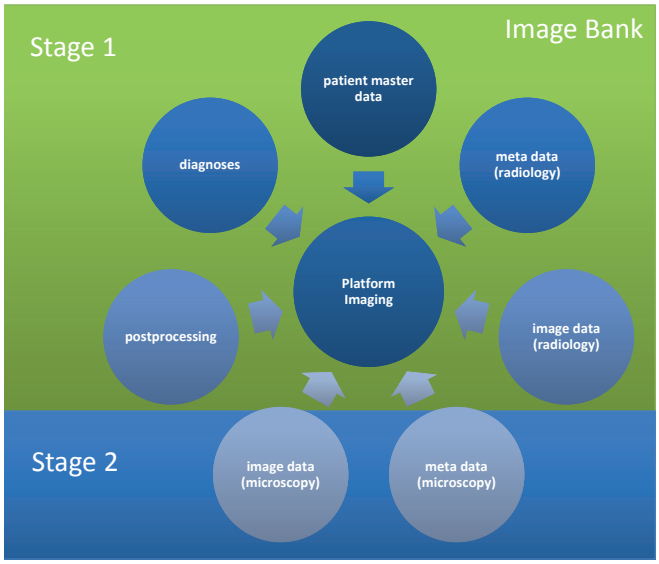
Solution

- Minium data set
- Database integration into DZL infrastructure
- Evaluation of commercial and open source software solutions
- Cooperation with Biobank

Goals in 2012

- Hard- and Software acquisation
- Hard- and Software installation
- Development of minimum dataset (radiology)
- Cooperation with sites and platforms
- Implementation of data management

The idea behind the Image Bank is to implement a central database containing information about imaging technologies, rule sets, SOPs, imaging data and a document management system. The Image Bank should be accessible from all sites with a user friendly graphical user interface, and the possibility of a query-retrieve system. In addition, the future system should also be able to load the image data automatically into the database and provide its own user management. To facilitate the query-retrieve system it is necessary to store the image data in a local database. Following systematic software evaluation, the appropriate hardware and software was acquired and installed in 2012. Furthermore, the minimum data set was developed and data management procedures were established. Because imaging data are difficult to be indexed, it is necessary to



load information about the imaging data (meta data) into the database. Based on this fact, a minimum data set was developed, which must be provided by all sites. The minimum data set consists of image meta data, patient master data, diagnoses and post-processing data.

The idea of a siloed software solution for the Image Bank was discarded in favor of integrating the image database into DZL infrastructure. The next step was the evaluation of possible commercial and open source software solutions. During the evaluation phase, there was extensive cooperation with the Platform Biobank because they have similar requirements for central services, such as a pseudonymization service.

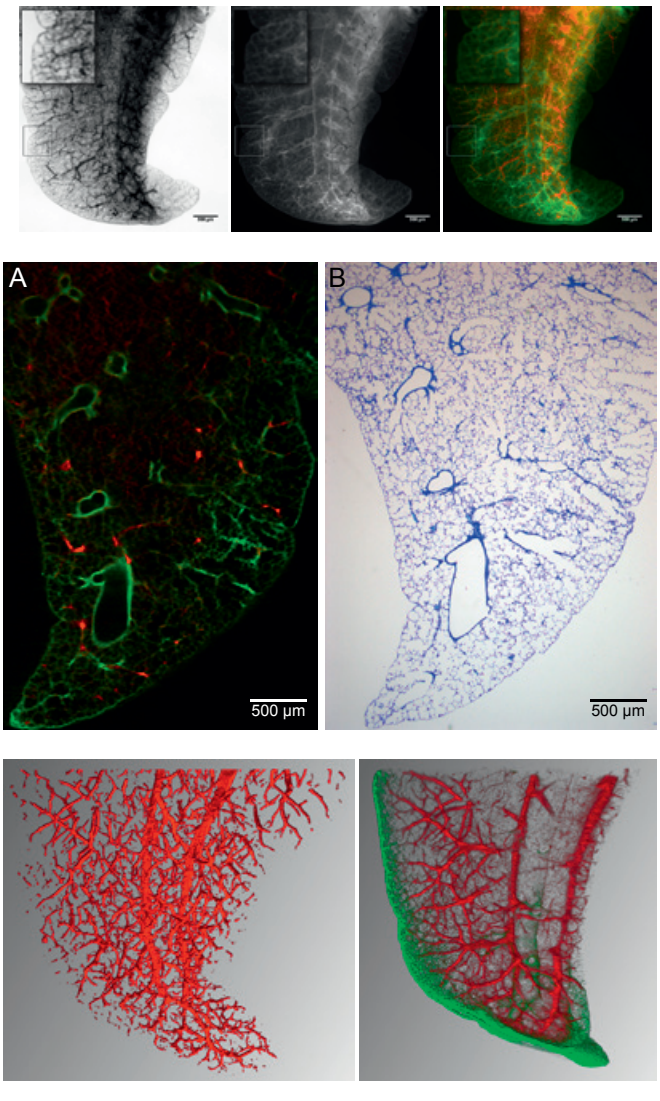
Research Highlight #1: Microscopy

Non-destructive ex vivo imaging of whole fixed mouse lungs by Scanning Laser Optical Tomography (SLOT).

Available imaging technology based on optical projection tomography was improved with regards to sensitivity (photon collection efficiency) by using a laser scanner. Following a newly developed lung preparation protocol, simultaneous acquisition of projection datasets in transmission and fluorescence mode with alveolar resolution is possible in less than 30 minutes (top row).

These datasets can be reconstructed to volumetric datasets with stacks of thin optical slices in any preferred spatial orientation (left middle row; compare histological section right), thus allowing quantitative (stereological) analysis and 3D reconstruction of structures of interest, e.g. blood vessels or individual acini (bottom row).

This approach is currently extended towards imaging of animal models of lung disease and clinical samples. (Figure from Kellner et al., J Appl Physiol 113 (6): 975, 2012 with permission from the American Physiological Society.)

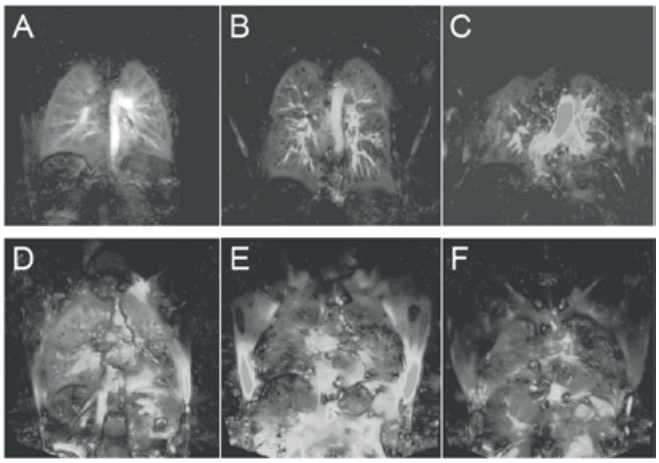


Research Highlight #2: Radiology

Non-contrast enhanced pulmonary perfusion and ventilation imaging

The management of respiratory diseases requires appropriate diagnostic tools providing both morphological and functional pulmonary assessment. Computed tomography (CT) is currently considered the standard of reference for evaluating lung morphology. With regards to function, pulmonary function tests (PFT) are readily available, however, they do not allow for spatial localization of lung pathologies. Recent research shows that detection of regional pulmonary perfusion and ventilation defects provides new insights and is rapidly gaining clinical importance for the diagnosis and follow-up of chronic lung diseases such as asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis or pulmonary hypertension, in which spatial heterogeneity of perfusion and ventilation is expected.

The Fourier decomposition (FD) method has been proposed for non-contrast-enhanced functional lung MRI. It was shown to be feasible to obtain regional perfusion and ventilation images of the lungs with neither contrast agent nor respiratory gating.



(Eur J Radiol 2013; 82: 1015-22)

Highlighted Publications - Microscopy:

1. Kellner M, Heidrich M, Beigel R, Lorbeer RA, Knudsen L, Ripken T, Heisterkamp A, Meyer H, Kühnel MP, Ochs M. Imaging of the mouse lung with scanning laser optical tomography (SLOT). J Appl Physiol 2012; 113:975-983
2. Vasilescu DM, Gao Z, Saha PK, Yin L, Wang G, Haefeli-Bleuer B, Ochs M, Weibel ER, Hoffman EA. Assessment of morphometry of pulmonary acini in mouse lungs by non-destructive imaging using multi-scale micro-computed tomography. Proc Natl Acad Sci USA 2012; 109:17105-17110
3. Röckendorf N, Borschbach M, Frey A (2012) Molecular evolution of peptide ligands with custom-tailored characteristics for targeting of glycostrucutures, PLoS Computational Biology 8 (12); e1002800

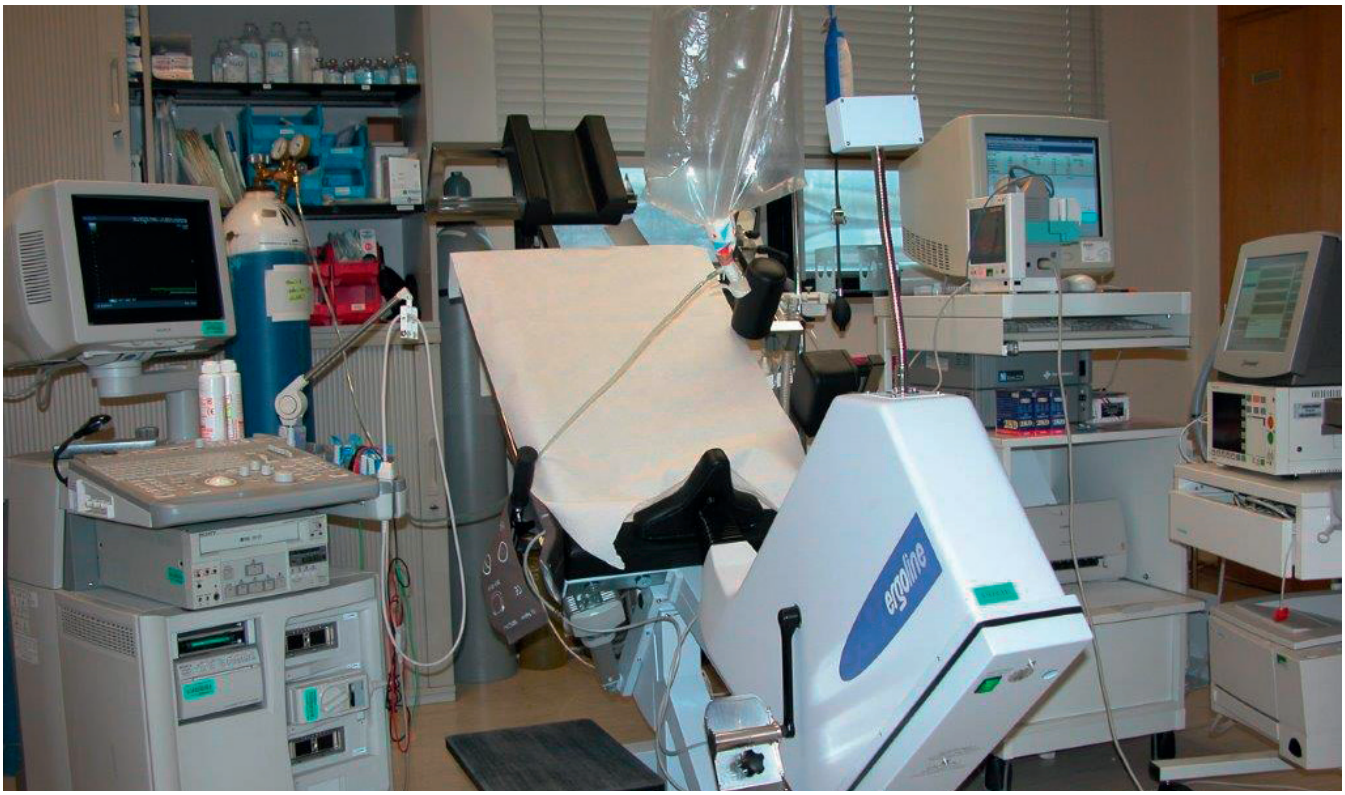
Highlighted Publications - Radiology:

1. Eichinger M, Optazaite DE, Kopp-Schneider A, Hintze C, Biederer J, Niemann A, Mall MA, Wielputz MO, Kauczor HU, Puderbach M. Morphologic and functional scoring of cystic fibrosis lung disease using MRI. Eur J Radiol 2012; 81:1321-1329.
2. Hopkins SR, Wielputz MO, Kauczor HU. Imaging lung perfusion. J Appl Physiol 2012; 113:328-339.
3. Koenigkam-Santos M, Puderbach M, Gompelmann D, Eberhardt R, Herth F, Kauczor HU, Heussel CP. Incomplete fissures in severe emphysematous patients evaluated with MDCT: incidence and interobserver agreement among radiologists and pneumologists. Eur J Radiol 2012; 81:4161-4166.

DZL Clinical Trial Board

Innovative science can often lead in unexpected directions. In order to be able to respond to new findings in the field and translate those findings as quickly as possible to positive outcomes for patients, a portion of the DZL budget was set aside for the funding of investigator initiated innovative clinical trials. Applications for funding are reviewed by the DZL Clinical Trial Board and their recommendations are reviewed and approved by the DZL Executive Board. In 2012 the following trials were funded:

- Randomized, double-blind, controlled pilot study on the safety of hypertonic saline as a preventative inhalation therapy in newborn patients with cystic fibrosis
  - Coordinating Investigator: M.A. Mall (TLRC)
- Comprehensive characterization of Non Small Cell Lung Cancer (NSCLC) by integrated clinical and molecular analysis
  - Coordinating Investigators: M. Thomas (TLRC), R.M. Huber (CPC-M)
- Clinical validation of the iNOS-EMAPII axis as biomarkers, predictors and novel targets in COPD
  - Coordinating investigators: R. Voswinckel (UGMLC), C. Vogelmeier (UGMLC)
- Clinical study to investigate safety, tolerability, efficacy, pharmacokinetics and pharmacodynamics of multiple doses of the human GATA-3-specific DNAzyme solution SB010 in patients with moderate to severe COPD - A randomised, double-blind, parallel, multicentre, pilot study
  - Coordinating Investigator: C. Vogelmeier (UGMLC)



Cooperation and Collaboration

DZL Kickoff Meeting, Frankfurt, 2012

Cooperation and collaborations are two hallmarks of the DZL. More than 50% of DZL funds were awarded to projects involving more than one Partner Center. Collaboration is facilitated by frequent Disease Area and Platform meetings, and the DZL annual meeting brings together DZL scientists across research areas to report on the latest updates and exchange ideas. The 2012 kickoff meeting in Frankfurt was attended by close to 200 DZL scientists. In addition, the DZL Executive Board, which contains representatives from all Partner Centers, meets weekly to discuss the latest findings, identify potential synergies, and provide leadership on a cross-functional, cross-locational basis.

The DZL is involved in several national research associations. In 2012 the DZL was an associate member of the Technology and Methods Platform for Network Research in Medicine (TMF e.V.), with full membership planned for 2013. All DZL researchers will have access to this resource. In addition, the DZL cooperates extensively with the German Society for Pneumology (DGP), co-editing the journal of this society ("Pneumologie"), publishing frequently latest DZL news in this journal and establishing a stipendium for young researchers at centers outside the DZL. On an international level, cooperation with INSERM was initiated in 2012 to establish a German-French Lung School.

Youth Development and Equal Opportunities

At the DZL measures to promote young researchers operate at several levels. Independent Junior Research Group Leadership and W2 Professorships have been advertised and the recruitment process is ongoing. At all DZL sites, young scientists are actively involved in national and international conferences, both within and external to the DZL. The establishment of a DZL/DGP Stipend for young researchers was announced in 2012, with the first award anticipated for 2013. In addition, the grant application for a DZL-wide German-French Lung School that will promote cooperation between lung researchers in Germany and France and provide international training opportunities for young researchers was submitted in 2012.

Young DZL scientists have access to the existing graduate training programs at each site. PhD students from ARCN have the opportunity to participate in a variety of graduate programs. The Universities of Kiel and Lübeck support students through their particular graduate centers. Moreover, there are two Graduate Programs (Graduiertenkolleg, GRK) at these universities that originated from the DFG Excellence Initiative, namely the GRK "Modulation of Autoimmunity" and the GRK "Genes, Environment, Inflammation." In both of these GRKs, content extends into the field of basic lung research. Finally, the Research Center Borstel conducts the Borstel Biomedical Research School (BBRS). The BBRS is an initiative fully devoted to lung research. It focuses on scientific topics as well as soft skills and includes a mentoring program for all PhD students at the institute.

At BREATH many of the medical and PhD students are involved in one of the programs offered at the Hannover Biomedical Research School (HBRS), for example, the doctoral programs "Molecular Science" or "Regenerative Medicine", or, in the case of the medical students, in the StrucMed program (Structured Medical Doctors' program). StrucMed is a unique program for medical students which includes 9 months of laboratory research. All programs involve scientific lectures as well as soft-skill courses, mentoring programs, and scientific events. In addition, all young scientists involved in DZL projects participate in BREATH's quarterly colloquia in which DZL PIs and members of their working groups present and discuss their DZL projects.

The Research School "Lung Biology and Disease," is an international, interdisciplinary and thematically focused doctoral training program established at CPC-M. Over a period of 3 years, MD and PhD students benefit from comprehensive teaching curricula and close mentorship while performing cutting edge research projects within one of the CPC-M research groups. Under supervision of highly experienced faculty members, students have the opportunity to investigate lung biology and disease at the interface of basic sciences and clinical medicine. As part of this program, students and faculty from the Helmholtz Zentrum München and the French organization INSERM (Institut National de la Santé et de la Recherche Médicale, Paris) came together in February of 2012 for the first German-French retreat on chronic lung disease. The Retreat resulted from the CPC-M and INSERM strategic plan to coordinate common educational programs in the field of chronic lung disease. Topic-specific seminars and lectures were given by invited faculty and guest speakers, and all doctoral students presented the progress of their research projects. During the Meet-the-Professor seminar, doctoral students could discuss their career plans and ask questions to experienced faculty members who gave them some advice for the future. A total of 135 participants, including representatives from several DZL Centers took part.

INSERM Retreat 2012

At TLRC medical doctoral and PhD students are enrolled in the The Hartmut Hoffmann-Berling International Graduate School of Molecular and Cellular Biology (HBIGS - http://www.hbigs.uni-heidelberg.de/). The structured PhD program includes training in state-of-the-art life sciences technologies in core courses as well as soft skill courses such as scientific writing and project management. The students' mentoring includes regular meetings with their thesis advisory committee. The training runs in parallel to their research project work embedded in the TLRC research program. Faculty members and junior researchers meet up for monthly research seminars with invited speakers from within the DZL as well as other national and international research institutions.

The UGMLC School is the umbrella program for the coordination of education and training of pulmonary scientists at the University of Giessen, the University of Marburg, and the Max Planck Institute of Heart and Lung Research in Bad Nauheim. Participating doctoral students at the Justus Liebig University in Giessen are also enrolled in the International Graduate Program, Molecular Biology and Medicine of the Lung, while participating doctoral students at the Max Planck Institute for Heart and Lung Research in Bad Nauheim are enrolled in the International Max Planck Research School for Heart and Lung Research. All enrolled students and associated faculty members benefit from a series of Scientific and Career Development Symposia organized within the framework of the UGMLC

Announcing the 6th Scientific Symposium of the University of Giessen and Marburg Lung Center School
22nd -23rd October, 2012

Perspectives on the Lung

What have we learnt – and where do we go?

Venue: Schlosshotel Romrod
36329 Romrod, Hessen, Germany

Scientific Organisers and Planning Committee
Rory E. Morty • Dorothea M. Peters • Florian Veit • Werner Seeger
from the University of Giessen and Marburg Lung Center

Capacity is Limited – Registration is Required
Information: www.uni-giessen.de/cms/ugmlc/symposia/perspectives
Enquiries: rory.morty@innere.med.uni-giessen.de

UGMLC Universities of Giessen & Marburg Lung Center · HESSEN · LOEWE – Landes-Offensive zur Entwicklung Wissenschaftlich-ökonomischer Exzellenz · DZL Deutsches Zentrum für Lungenforschung

All images used with permission: Schlosshotel Romrod (Deutschen Stiftung Denkmalschutz) and Shutterstock (masked physician)

Announcing the 7th Scientific Symposium of the University of Giessen and Marburg Lung Center School
12th – 13th November, 2012

Programming the Lung

Epigenetic control of lung biology through histone and chromatin modification

Venue: Schlosshotel Weilburg
35781 Weilburg, Hessen, Germany

Scientific Organisers and Planning Committee
Rory E. Morty • Dorothea M. Peters • Florian Veit • Werner Seeger
from the University of Giessen and Marburg Lung Center

Capacity is Limited – Registration is Required
Information: www.uni-giessen.de/cms/ugmlc/symposia/programming
Enquiries: rory.morty@innere.med.uni-giessen.de

UGMLC Universities of Giessen & Marburg Lung Center · HESSEN · LOEWE – Landes-Offensive zur Entwicklung Wissenschaftlich-ökonomischer Exzellenz · DZL Deutsches Zentrum für Lungenforschung

All images used with permission: Schlosshotel Weilburg (Schloß) and Shutterstock (DNA strand)

School. In 2012, all DZL junior scientists were invited to specialized "UGMLC-DZL school symposia", with internationally renowned faculty serving for each of this symposium. The topics in 2012 were:

- Developing the Lung
- Funding the Lung
- Perspectives on the Lung
- Programming the Lung

Measures to ensure equal opportunities are carried out in close cooperation with the appropriate bodies of DZL-partner sites. In the context of gender equality programs of the participating university partners and others, priority will be placed on the active recruitment of female scientists to the DZL at every level – from the trainee to the advisory board member.

Public Relations and Awards

Public Relations

The DZL employs a multi-faced approach towards public outreach. The Lung Information Service (LID), headquartered at the Helmholtz Center in Munich makes new research findings and patient information available to the general public through its website www. lungeninformationsdienst.de and expert forums. DZL scientists play a significant advisory role in the work of the LID by participating in expert forums as well as contributing to LID publications. In 2012 DZL scientists participated e.g. in the LID patient forums on childhood asthma and on pulmonary hypertension.

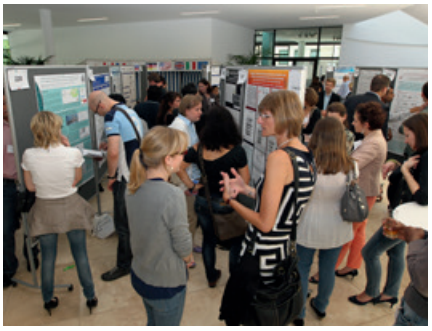
In addition, two press conferences were held by the DZL, one in Berlin in March to celebrate “100 Days of the DZL” and a second in Vienna in September 2012 in conjunction with the annual meeting of the European Respiratory Society. Both press conferences were opportunities to showcase DZL research plans and accomplishments. The DZL is also a frequent contributor to the journal “Pneumologie” with two DZL-related features being published in 2012. A feature about the DZL was also published in 2012 in the international medical journal, The Lancet. Finally, a newly designed DZL website www.dzl.de was launched in 2012.

Awards

In December 2012 it was announced that Prof. Dr. Erika von Mutius of University of Munich (LMU) and a DZL investigator at CPC-M is one of 11 recipients of the 2013 Leibnitz Prize. She was recognized for her work relating to the development and treatment of lung disease in children, in particular for her fundamental work involving allergic asthma in children. Dr. Von Mutius discovered that hygienic conditions for newborns and small children play a significant role in the formation of allergies.

Other prizes awarded to DZL researchers include a Europe ASPIRE Award in Antifungal Research - a Competitive Grants Program for investigators in Europe (Title “Retrospective Interdisciplinary Multicentre Analysis of Fungal Pneumonia in Children”) to Prof. Dr. Claus Peter Heußel of TLRC and the Felix-Wachsmann-Prize of the German Academy of Continuous Education in Radiology, also to Prof. Dr. Heußel. Nicolas Kahn of TLRC received the Ludolf-Krehl-Prize 2012 from the South-West German Society of Internal Medicine for his dissertation entitled, “ Gen-Expressions-Analysen aus endobronchialer epithelialer Flüssigkeit zur Abklärung pulmonaler Rundherde” (Gene expression analyses in endobronchial epithelial lining fluid for the early detection of pulmonary lesions).

International Symposium 2012



In June 2012 the DZL hosted its first international symposium in conjunction with Universities of Giessen and Marburg Lung Center (UGMLC). From June 21 – 23 more than 250 conference participants attended the symposium "Remodeling, Repair and Regeneration in Lung Diseases" held at the idyllic Rosenpark Conference Center in Marburg. Some of the world's leading lung researchers including DZL Scientific Advisory Board Member Peter Barnes (Imperial College London), Leo Fabbri (University of Modena & Reggio Emilia), Kurt Stenmark (University of Colorado Denver) and Joe Garcia (University of Illinois at Chicago) presented current research findings relevant across a number of DZL disease areas. A highlight of the conference program was the "Editor Session" where renowned editors of top journals in the fields of pulmonary research, allergy, and clinical immunology presented tips to young scientists about how to help ensure that their papers would be published. More than 100 posters were presented by DZL scientists and the DZL Disease Areas took advantage of the meeting to hold face-to-face satellite Disease Area meetings.

The German Centers for Health Research

The main objective of the German government's framework program for health research is to more effectively combat complex common diseases that are becoming increasingly prevalent in the population. To create favorable conditions for achieving this goal, the Federal Ministry of Education and Research has established the German Centers for Health Research. These Centers have been set up as long-term, equal partnerships between non-university research institutions and universities with university hospitals.

The German Centers for Health Research leverage existing competencies and thus make a significant contribution to closing knowledge gaps and to improving prevention, diagnosis and treatment. The aim is to achieve the highest possible level of therapeutic efficacy for each patient. The Centers' research policy emphasizes close cooperation between the basic and clinical research units of all partners, oriented on the indications and the needs of the patients. The close networking and expansion of existing research structures enable a faster transfer of research findings into clinical practice (translational research).

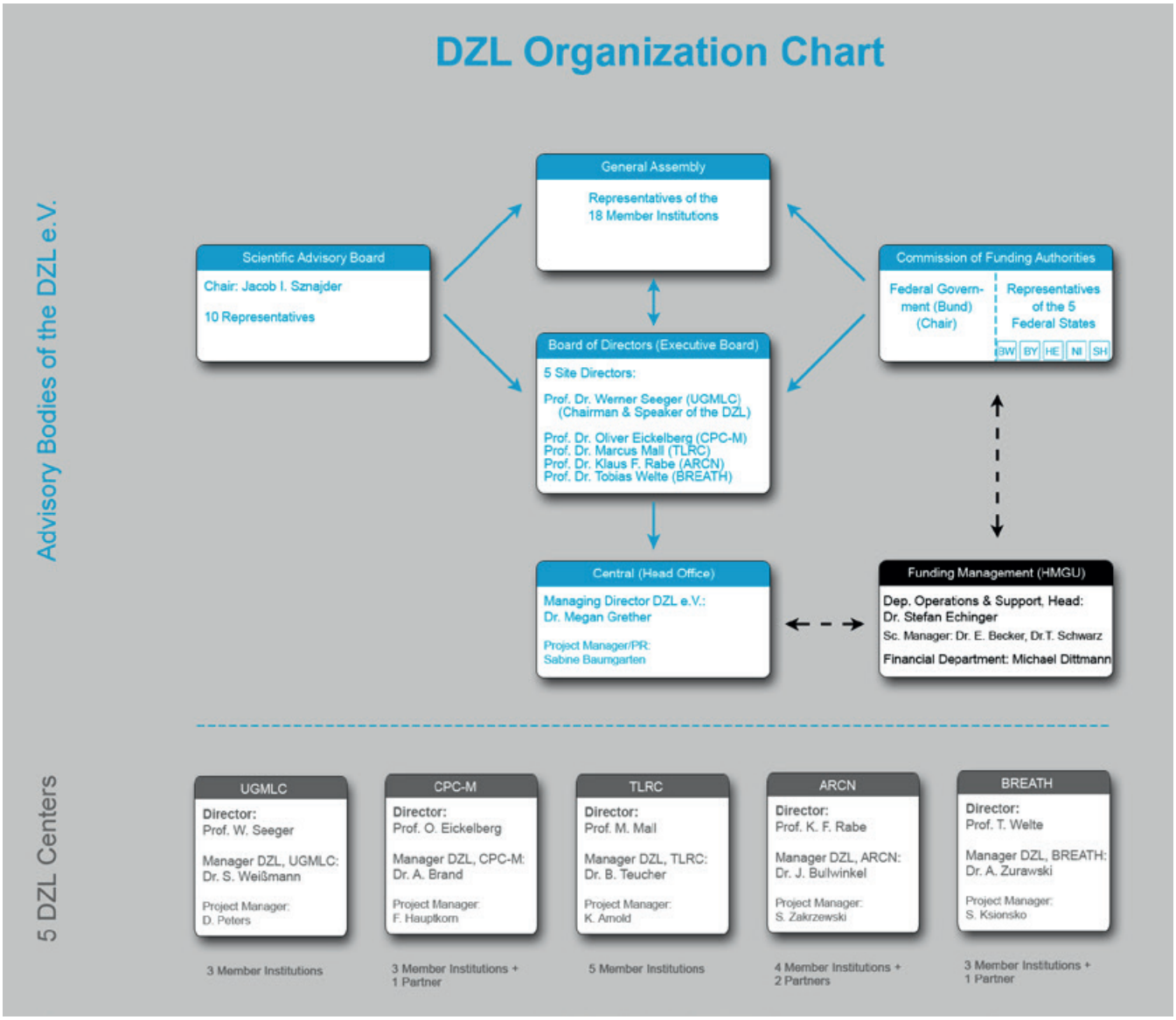
Over the long term, the strategic collaboration of leading scientists in the German Centers for Health Research will make Germany internationally more competitive as a science location and markedly more attractive for young researchers both within Germany and from around the world.

In 2009 the German Center for Neurodegenerative Diseases (DZNE) and the German Center for Diabetes Research (DZD) were founded. In 2011 four additional German Centers for Health Research were established: the German Center for Infection Research (DZIF), the German Center for Cardiovascular Research (DZHK), the German Consortium for Translational Cancer Research (DKTK) and the German Center for Lung Research. A steering committee in which all partners participate coordinates the joint research activities as well as the division of tasks and use of resources for all sites of the respective center, in accordance with the jointly defined research priorities.

DZL Organization

In the DZL more than 170 principal investigators and their research groups work together to combat lung disease. These scientists are located at 22 top research institutes throughout Germany, and their activities are managed by five coordinating centers

The DZL is overseen by a five member Board of Directors, and an International Advisory Board provides input on scientific strategy. The DZL General Assembly and Commission of Funding Authorities are also important governing bodies of the DZL. The scientific and administrative activities of the DZL are coordinated by the central Head Office in Giessen in conjunction with the local Managers. Financial administration is managed by the Funding Management Office based at the Helmholtz Center in Munich.



DZL Head Office

The head office of the German Center for Lung Research is located at Justus-Liebig University in Giessen. It supports the work of the Board, is responsible for the coordination and implementation of DZL programs, coordinates internal and external communications, and is the point of contact for all matters relating to the DZL. The five site managers work in close collaboration with the DZL Head Office to support and coordinate the work of the DZL.

Chairman and Speaker of the DZL, Director of the UGMLC site: Prof. Dr. Werner Seeger

Managing Director:

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Project Coordinator/Public Relations:

Sabine Baumgarten
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DZL Board of Directors

The DZL is led by a five member Board of Directors, one from each DZL partner site. The Chairman and Speaker of the DZL Board is Prof. Dr. Werner Seeger of the UGMLC site. The other Board members are Prof. Dr. Oliver Eickelberg (CPC-M), Prof. Dr. Marcus A. Mall (TLRC), Prof. Dr. Klaus F. Rabe (ARCN), and Prof. Dr. Tobias Welte (BREATH).

Funding Management Office

The Funding Management Office is located at the Helmholtz Center in Munich. It is responsible for management of funds for the DZL from the Federal Ministry of Education and Research (BMBF). The Funding Management Team includes the Head of the Department of Operations and Support, Dr. Stefan Echinger, Scientific Managers Dr. Eva Becker and Dr. Tobias Schwarz, and Michael Dittmann, Claudia Fricke, and Katrin-Alexandra Pickl of the Financial Department.

Commission of the Funding Authorities

The Commission of Funding Authorities (Kommission der Zuwendungsgeber, KdZ) oversees the DZL's cooperation with the DZL granting agencies. 90% of the DZL funds are provided by the Federal Ministry for Education and Research (Bundesministerium für Bildung und Forschung, BMBF) with the remaining 10% coming from the respective states (Länder) in which a funded institution is located. The BMBF and the states each send a representative to the KdZ, which is chaired by a representative of the federal government. States contributing funds to the DZL are Baden-Württemberg, Bavaria, Hesse, Lower Saxony, and Schleswig-Holstein.

DZL General Assembly

The General Assembly (Mitgliederversammlung) is the central decision-making body of DZL. It is composed of representatives from each of the 18 DZL member institutions. The General Assembly elects the members of the Board of Directors and the Board Chair. On the basis of proposals from the DZL Board of Directors, the General Assembly decides on issues of fundamental importance to the DZL including determination of scientific priorities, allocation of responsibilities amongst the sites, and the proposed use of resources in accordance with reviewer recommendations.

DZL Scientific Advisory Board

The DZL is honored to have a distinguished board of internationally renowned experts as advisors.

Professor Peter J Barnes
Head of Respiratory Medicine, Imperial College London

Professor Rachel Chambers
Professor of Respiratory Cell and Molecular Biology, Center for Respiratory Research, University College London

Jeffrey M Drazen, MD
Distinguished Parker B. Francis Professor of Medicine, Harvard Medical School; Editor-in-Chief, New England Journal of Medicine

Professor Stuart Elborn
Professor of Respiratory Medicine, Director CF Center, Belfast City Hospital, President ECFS, Centre for Infection and Immunity, Queen's University Belfast

Mark Gladwin, MD
Division Chief, Pulmonary, Allergy, and Critical Care Medicine, Director Vascular Medicine Institute, University of Pittsburgh Medical Center

Marlene Rabinovitch, MD
Professor of Pediatric Cardiology, Stanford University School of Medicine

Susan Shurin, MD
Deputy Director, National Heart, Lung, and Blood Institute (NHLBI), National Institutes of Health (NIH)

Stephen G Spiro, MD
Honorary Physician, University College London Hospitals and The Royal Brompton Hospital

Peter M. Suter, MD
Akademien der Wissenschaften Schweiz, Centre Medical Universitaire, University of Geneva

Jacob I Szajdner, MD
Chief, Division of Medicine-Pulmonary, Ernest S. Bazley Professor of Asthma and Related Disorders, Northwestern University Feinberg School of Medicine

DZL Coordinating Centers

BORSTEL/LÜBECK/KIEL/GROßHANSDORF

AIRWAY RESEARCH CENTER NORTH (ARCN)

Forschungszentrum Borstel

Universität zu Lübeck

Universitätsklinikum Schleswig-Holstein – Campus Lübeck

Universitätsklinikum Schleswig-Holstein – Campus Kiel

Christian-Albrechts-Universität zu Kiel

LungenClinic Grosshansdorf

DIRECTOR

Prof. Dr. Klaus F. Rabe

HANNOVER

BIOMEDICAL RESEARCH IN ENDSTAGE AND OBSTRUCTIVE LUNG DISEASE HANNOVER (BREATH)

Medizinische Hochschule Hannover

Leibniz Universität Hannover

Fraunhofer-Institut für Toxikologie und Experimentelle Medizin in Hannover

CAPNETZ Stiftung

DIRECTOR

Prof. Dr. Tobias Welte

GIEßEN/MARBURG/BAD NAUHEIM

UNIVERSITIES OF GIESSEN AND MARBURG LUNG CENTER (UGMLC)

Justus-Liebig-Universität Gießen

Philipps-Universität Marburg

Max-Planck-Institut für Herz- und Lungenforschung in Bad Nauheim

DIRECTOR

Prof. Dr. Werner Seeger
Speaker and Chairman of the DZL

HEIDELBERG

TRANSLATIONAL LUNG RESEARCH CENTER (TLRC)

Universitätsklinikum Heidelberg

Ruprecht-Karls-Universität Heidelberg

Thoraxklinik am Universitätsklinikum Heidelberg

Deutsches Krebsforschungszentrum (DKFZ)

European Molecular Biology Laboratory (EMBL)

DIRECTOR

Prof. Dr. Marcus A. Mall

MUNICH

COMPREHENSIVE PNEUMOLOGY CENTER MUNICH (CPC-M)

Helmholtz Zentrum München – Deutsches Forschungszentrum für Gesundheit und Umwelt

Ludwig-Maximilians-Universität München

Klinikum der Universität München

Asklepios Fachkliniken München-Gauting

DIRECTOR

Prof. Dr. Oliver Eickelberg

DZL Coordinating Centers

In the DZL more than 170 principle investigators and their research groups work together to combat lung disease. These scientists are located at 22 top research institutes throughout Germany, and their activities are managed by five coordinating centers: Airway Research Center North (ARCN), Biomedical Research in Endstage and Obstructive Lung Disease Hannover (BREATH), Comprehensive Pneumology Center Munich (CPC-M), Translational Lung Research Center Heidelberg (TLRC), and the Universities of Giessen and Marburg Lung Center (UGMLC).

Research efforts are focused on eight disease areas: asthma and allergy, chronic obstructive pulmonary disease, cystic fibrosis, pneumonia and acute lung injury, diffuse parenchymal lung disease, pulmonary hypertension, endstage lung disease, and lung cancer.

Scientists across different sites use an integrated and synergistic approach to combat these disorders. The integrated scientific approach being put into practice explores the dynamic relations among 1) generation, regeneration, repair; 2) inflammation resolution; and 3) hyperproliferation across all DZL disease areas.

Each site is equipped with the expertise and infrastructure necessary to explore disease mechanisms in detail. Cooperation as well as constant exchange of information and ideas among the research sites means that findings at one site can be rapidly capitalized on by researchers at other locations.

Every disease area studied engages scientists at three to five of the DZL coordinating centers, and these cross-center research efforts are supported by access to DZL-wide infrastructure. Findings in one disease area may be applicable across several disease areas, and the DZL scientific approach and infrastructure allow for rapid translation of findings across diseases.

Airway Research Center North (ARCN)

Borstel, Lübeck, Kiel, Grosshansdorf

- Research Center Borstel
- University of Lübeck
- University Clinic Schleswig-Holstein, Lübeck Campus
- University Clinic Schleswig-Holstein, Kiel Campus
- Christian Albrechts University Kiel
- LungenClinic Grosshansdorf

Prof. Dr. Klaus F. Rabe

- Director of ARCN
- Medical Director of the LungenClinic Grosshansdorf
- Professor of Pneumology, Christian Albrechts University Kiel
- Chairman of the DGP Institute for Lung Research (ILF)
- President of the European Respiratory Society (ERS) 2011 / 2012

Contact

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Number of DZL Principal Investigators: 24

Research Profile

Scientists and clinicians of the Airway Research Center North (ARCN) focus on research on chronic obstructive pulmonary disease (COPD), lung cancer as well as asthma and allergy. This translational research consortium combines top level expertise in basic research and medicine in the field of pulmonology in Schleswig-Holstein. Together with its partners in the DZL, ARCN aims to find more effective ways to prevent disease, to provide earlier diagnoses, and to develop enhanced, individualized therapies for patients with lung disease. In keeping with the approach of the DZL, ARCN researchers pursue a holistic approach to study of the lung, including studying disease pathogenesis, the progression of inflammatory and proliferative processes, and the regeneration and/or repair of diseased lung tissue.

As the biggest North-German clinic specialized in lung and airway diseases with more than 13,000 patients treated per year, LungenClinic Grosshansdorf, together with the University Clinic Schleswig-Holstein (UKSH) and the Medical Clinic Borstel, is responsible for clinical and patient-oriented research in ARCN. The Research Center Borstel is devoted to investigation of infectious as well as non-infectious lung diseases and is key to the success of ARCN basic research and animal models. Additional partners are researchers at the University of Lübeck and the Christian-Albrechts-University Kiel. These scientists test asthma in animal models, analyze the epigenetic background of lung diseases and develop novel imaging techniques.

To strengthen the connection between clinical and basic research, the Biomaterialbank Nord has been installed as central infrastructure. This crosslink between complementary partners in ARCN is intended to support the collaborative implementation of translational research strategies.

Biomedical Research in Endstage and Obstructive Lung Disease Hannover (BREATH)

Hannover

- Hannover Medical School (MHH)
- The Fraunhofer Institute for Toxicology and Experimental Medicine (ITEM)
- Leibnitz Universität Hannover
- CAPNETZ Stiftung

Prof. Dr. Tobias Welte

- Director of BREATH
- Chairman of the German Sepsis Society
- Speaker for the Clinical Study Center Hannover (KS-MHH) (set up by the BMBF)
- Member of the Presidium of the German Interdisciplinary Association for Intensive Care and Emergency Medicine (DIVI)
- Chairman of the Board of Trustees of the CAPNETZ Stiftung
- Head of the Competence Center for Infectious Diseases
- Director of the Competence Network ASCONET
- President of the German Society of Pneumology

Contact

- DZL Manager, BREATH: Dr. Annegret Zurawski
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Number of DZL Principal Investigators: 42

Research Profile

In the BREATH research network, doctors and scientists from Hannover Medical School (MHH), the Fraunhofer Institute for Toxicology and Experimental Medicine (ITEM), the Center for Health Economics Research Hannover (CHERH) of the Leibniz Universität Hannover (LUH), and the CAPNETZ Stiftung have come together to carry out research in the field of lung diseases with the aim of optimizing the care structure for patients, including gaining new knowledge, developing and expanding current therapeutic measures, stemming and reducing mortality in this field and generally improving the quality of life of patients with lung diseases. There is also close cooperation with the REBIRTH Cluster of Excellence. A major focus of BREATH is clinical research, particularly in the fields of lung transplantation and stem cell therapy. In 2012 at the Hannover Medical School, DZL scientists from BREATH were involved in the first living lung donation in Germany.

The Department of Respiratory Medicine at MHH is engaged in the lung transplantation program and conducts research in the fields of infectious disease, allergic disease, and pulmonary hypertension. Basic research on infectious diseases focuses on inflammatory cells in the pulmonary system and on proteolytic enzymes in connection with infection. In cooperation with Fraunhofer ITEM, research scientists investigate the pathophysiology of allergic diseases and have access to the cutting edge pollen exposure room at ITEM. Researchers at LUH bring significant expertise in the fields of health services and health economics to the DZL. Finally, the nation-wide research network, CAPNETZ (Network of Excellence Community Acquired Pneumonia), is now integrated into the DZL. CAPNETZ connects clinical, microbiological and basic research in order to gain knowledge about the pathogenesis of community acquired pneumonia (CAP), a significant public health challenge. CAPNETZ is the most comprehensive CAP database in the world.

Comprehensive Pneumology Center Munich (CPC-M)

Munich

- Helmholtz Center Munich – German Research Center for Environmental Health
- Ludwig Maximilians University Munich
- University of Munich Clinic
- Asklepios Clinic Munich-Gauting

Prof. Dr. Oliver Eickelberg

- Director of CPC-M
- Chairman of the Comprehensive Pneumology Center
- Director of the Institute for Lung Biology, Helmholtz Center Munich
- Professor of Experimental Pneumology at Ludwig-Maximilians-University of Munich (LMU)

Contact

- DZL Manager, CPC-M: Dr. Antje Brand
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- Tel.: +49 (0)89 3187-4670

Number of DZL Principal Investigators: 32

Research Profile

At the Comprehensive Pneumology Center Munich (CPC-M), the Helmholtz Center Munich - German Research Center for Environmental Health, Ludwig-Maximilians-University with its University Hospital, and the Asklepios Clinic Munich-Gauting come together to form one of the largest centers for translational research on chronic lung diseases world-wide. The Helmholtz Center Munich is a renowned expert in bridging fundamental experimental research and applied medical research. Ludwig Maximilians University is one of the top level universities in the German Excellence Initiative, and its medical faculty is involved in high level pulmonary research and medical care. The Asklepios Clinic Munich-Gauting is one of the leading hospitals in Germany that specializes in lung diseases.

Research at CPC-M is focused on chronic lung diseases. CPC-M scientists integrate state of the art techniques in molecular and cell biology, pharmacology, molecular pathology and clinical medicine in order to develop new diagnostic tools and therapies for chronic lung diseases. In addition to its research program, CPC-M scientists are coordinators for the disease areas “Diffuse Parenchymal Lung Disease (DPLD) and “Asthma and Allergy”. The German French Lung School is coordinated in Munich, together with the CPC Graduate Research School “Lung Biology and Disease.” The CPC-M also operates the Lung Information Service (www.lungeninformationsdienst.de) which is responsible for effective public education and outreach about lung diseases.

Translational Lung Research Center (TLRC)

Heidelberg

- University Hospital Heidelberg
- Ruprecht-Karls-University, Heidelberg
- Thorax Clinic at the University Hospital Heidelberg
- German Cancer Research Center
- European Molecular Biology Laboratory (EMBL)

Prof. Dr. Marcus A. Mall

- Director of TLRC
- Chairman of the Translational Lung Research Center
- Director of the Department of Translational Pulmonology
- Head of the Division of Pediatric Pulmonology & Allergy and Cystic Fibrosis Center

Contact

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Number of DZL Principal Investigators: 23

Research Profile

The Heidelberg Translational Lung Research Center (TLRC) is an interdisciplinary center for translational lung research in which physicians and scientists at the University Hospital and Medical Faculty of the University of Heidelberg, the Thorax Clinic at the University Hospital (one of Germany's largest hospitals specialized on lung diseases), the German Center for Cancer Research, and the European Molecular Biology Laboratory work together to combat lung disease. The common goal is to improve the diagnosis and treatment of chronic lung diseases in children and adults.

The research focus at the TLRC is on elucidating the mechanisms underlying the three common chronic and malignant lung diseases: cystic fibrosis (CF), COPD, and lung cancer. The scientists' goal is to identify new therapeutic targets to improve early diagnosis and develop more curative treatment options. Within the basic research program animal models are used to investigate molecular causes of chronic airway diseases with a focus on the role of the airway epithelium. Results from these experiments will improve our understanding of airway mucous obstruction and chronic inflammation in CF and other chronic obstructive lung diseases, such as COPD and asthma. Another focus of research at the TLRC is the use of systems biology to better understand the molecular causes of lung cancer. New diagnostic and therapeutic strategies are under investigation at the TLRC in early clinical trials in order to make them available to patients in a timely manner.

Universities of Giessen and Marburg Lung Center (UGMLC)

Giessen/Marburg/Bad Nauheim

- Justus-Liebig University Giessen
- Philipps University Marburg
- Max Planck Institute for Heart and Lung Research in Bad Nauheim

Prof. Dr. Werner Seeger

- Chairman and Speaker of the German Center for Lung Research (national center)
- Director of UGMLC
- Managing Director of the Department for Internal Medicine, Justus Liebig University Giessen
- Director, Department of Lung Development and Remodeling, Max Planck Institute for Heart and Lung Research
- Director of the Excellence Cluster “Cardio-Pulmonary System” (ECCPS)

Contact

- DZL Manager, UGMLC: Dr. Sylvia Weissmann
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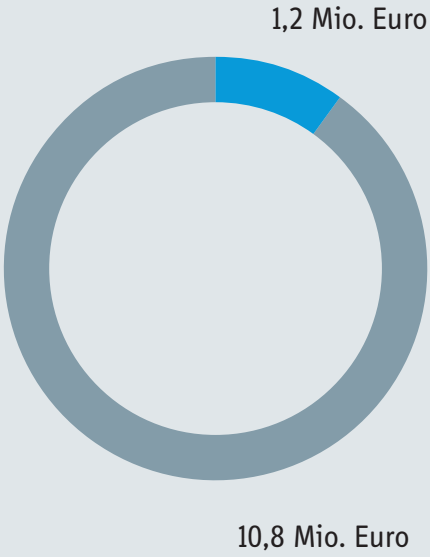
Number of DZL Principal Investigators: 50

Research Profile, UGMLC

Translational research at the Universities of Giessen and Marburg Lung Center (UGMLC) deals with lung diseases caused by inflammatory and hyperproliferative processes. At UGMLC, the entire research spectrum is covered, from the study of disease mechanisms at the molecular and cellular level to research in the clinic, with the ultimate aim of developing innovative therapeutics for patients. Pulmonary hypertension, pneumonia and respiratory failure, COPD and pulmonary fibrosis are the research areas of focus of DZL scientists at Justus Liebig University Giessen. The University Hospital is also an international treatment center for these diseases. DZL scientists at Philipps University Marburg mainly focus on asthma and allergy and COPD. The clinical areas there are linked to national disease networks (Asconet , Cosyconet). The Max Planck Institute for Heart and Lung Research in Bad Nauheim complements the clinical and translational science with basic research in the fields of stem cell research, developmental biology and cell signaling pathways.

In the disease area asthma, UGMLC researchers explore the influence of environmental factors, both before and after birth, on the development of disease. COPD research is focused on airway and vascular remodeling associated with chronic lung disease. For pneumonia and acute lung injury, the focus is on the role of innate immunity and inflammation in disease resolution and tissue repair. In the areas of lung fibrosis and pulmonary hypertension disease mechanisms are explored to develop effective regenerative therapies. To enable better treatment of end-stage lung disease, the UGMLC team is involved in projects to improve ECMO as a transition to lung transplantation. Cooperation with the other sites of the DZL plays a prominent role in all areas of research at UGMLC and UGMLC takes on a central coordinating role of common research networks and platforms such as the DZL Biobank.

Financials and Personnel

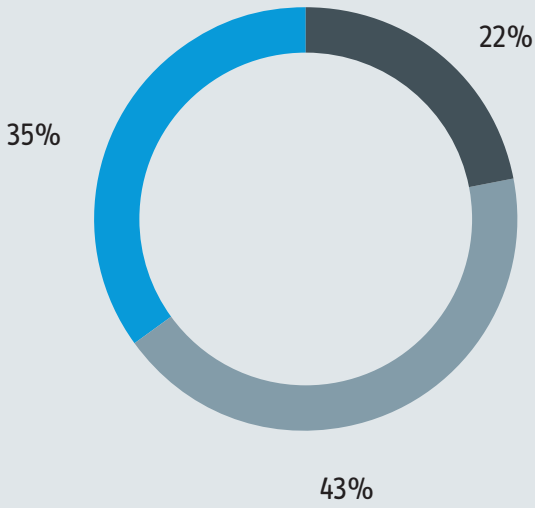


Total Funding

The total funding for the DZL in 2012 was 12 Million Euro. 90% was received from the Federal government and 10% from the states with participating DZL Centers. The Funding Management Office at the Helmholtz Center Munich distributed the project funding to the respective partner institutions.

The total budget 2012 includes pre-financing of equipment.

- Federal Government
- States (Baden-Württemberg, Bavaria, Hesse, Lower Saxony, Schleswig-Holstein)

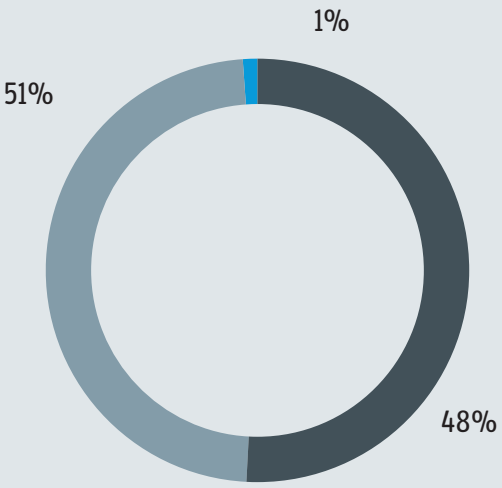


Cost Breakdown – DZL 2012 Expenses

The high portion of funds spent on equipment is due to the pre-financing of equipment at four partner sites by the Helmholtz Center Munich

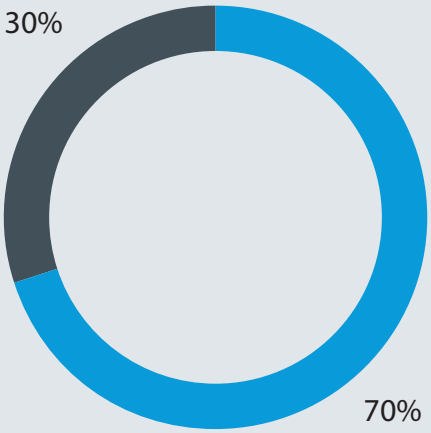
- Consumables
- Equipment
- Personnel

Cost Breakdown – DZL e.V. Expenses



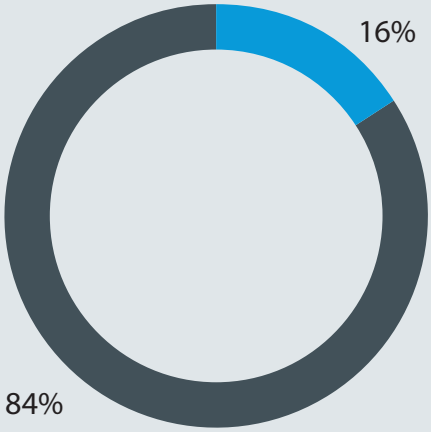
The DZL e.V. is financed through membership fees from each partner institution, amounting to €325,000 in 2012. The 2012 Annual Financial Statement and Year-end Close of the DZL e.V. was prepared by the firm Haas & Haas.

- Consumables
- Equipment
- Personnel



DZL Total Employees

- Male DZL Employees
- Female DZL Employees



DZL Faculty

- Male DZL Faculty
- Female DZL Faculty

Personnel and Equal Opportunities

In 2012 166 employees were financed with DZL funds across the five partner centers. Of these, 87 were scientists and 79 support staff. Of funded employees, 70% were women and 30% were men. However, of DZL Faculty members (DZL PIs) only 16% are women. The DZL is committed to increasing the number of women in faculty positions.

Patents

DZL Scientists are actively involved in translating research discoveries into inventions.
Patent activity in 2012 included:

BREATH (MHH)	Patent application in the disease area end-stage lung disease from 2011 – decision pending "Novel method for the production of respiratory epithelial cells" (EP 11000958.6, WO/2012/104400).
TLRC (Ruprecht-Karls-University Heidelberg)	US-provisional Application Nr. 61-650,000 Title: "Therapeutic Micro RNA targets in chronic pulmonary disease" Inventors: Marcus A. Mall, Raman Agrawal, Martina Muckenthaler.
UGMLC (Justus Liebig University Giessen)	Published patent: "Composite materials loaded with therapeutic and diagnostic agents comprising polymer nanoparticles and polymer fibres" Inventors: Schmehl T, Nguyen J, Beck-Broichsitter M; Gessler T, Kissel T, Thieme M. EP000002408438A2, Publication Date: 25.01.2012
UGMLC (Justus Liebig University Giessen)	Published patent: "Polymer nano- and micro-particles for the maintenance of the low surface tension in the lung and for the protection of the pulmonary surfactant." Inventors: Beck-Broichsitter M, Schmehl T, Gessler T. EP000002407150A1, Publication Date: 18.01.2012

Masthead

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Prof. Dr. Tobias Welte

Managing Director
Megan Grether, PhD

Content
German Center for Lung Research (DZL e.V.)

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Ministerium für Bildung
und Wissenschaft
des Landes Schleswig-Holstein

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