DZL
Deutsches Zentrum für Lungenforschung

DZG DEUTSCHE ZENTREN DER GESUNDHEITSFORSCHUNG

German Center for Lung Research

ANNUAL REPORT

2014

Translational Research to Combat Widespread Lung Diseases

Table of Contents

Foreword

Prof. Dr. Werner Seeger
Chairman and Speaker

Prof Dr. Klaus F. Rabe

Prof. Dr. Tobias Welte

Prof. Dr. Marcus Mall

Prof. Dr. Oliver Eickelberg

Diseases of the respiratory system are some of the most critical challenges of today's health care system. The World Health Organization lists four lung diseases among the top ten causes of death on a global level, accounting for close to 10 million deaths annually. Direct primary and hospital healthcare costs in Europe alone account for at least €55 billion of annual expenditure, and when factoring in lost production and disability-adjusted-life-years, the costs rise to more than €380 billion. In spite of the critical need, currently available treatments for most respiratory diseases provide symptomatic relief but no cure. These data highlight the urgent need to combat respiratory diseases in a concerted, innovative fashion. With its mission of using "Translational Research to Combat Widespread Lung Diseases" the German Center for Lung Research (Deutsches Zentrum für Lungenforschung, DZL) continues to make great strides against some of the world's biggest killers. In this report we summarize a lot of achievements of the DZL since its inception. Please read further to learn more about the DZL and what it is doing to fight respiratory diseases.

On behalf of the DZL,

About the DZL: Science – Translation in Focus

Founded in 2011, the German Center for Lung Research (Deutsches Zentrum für Lungenforschung, DZL) is one of six German Centers for Health Research (Deutsche Zentren der Gesundheitsforschung, DZG). Supported by German Federal and State Governments, the DZL brings together leading scientists and clinicians in the field of pulmonary research throughout Germany, all united with the aim of developing innovative new therapies for patients with lung disease.

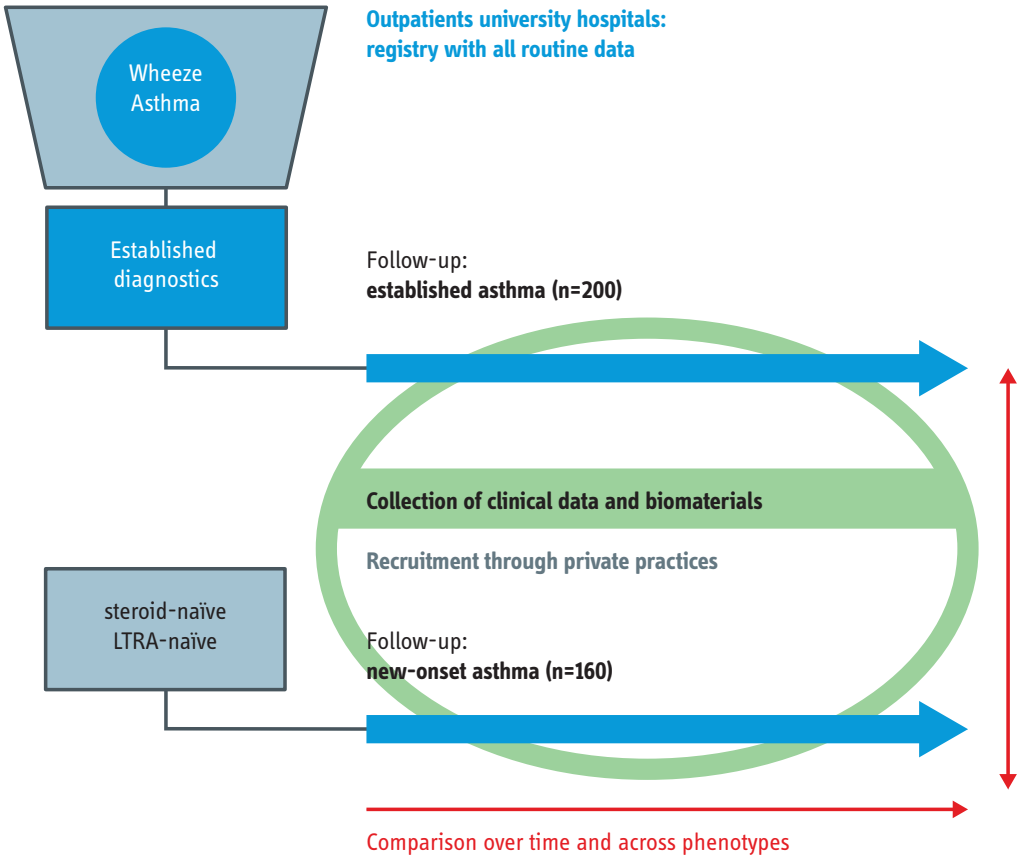
In 2014 the DZL included 210 principal investigators and their research groups. These top pulmonary researchers are working together to fight respiratory disease through translational research. DZL scientists are located at 22 premier research institutions throughout Germany, and their activities are managed by five cooperating 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 in the DZL 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. For each of the diseases studied by DZL scientists, the entire "bench-to-bedside" and – vice versa – "bedside-to-bench" translational research chain is applied. Basic science findings inform design and implementation of clinical trials and patient care, and clinical needs drive the basic science questions tackled by DZL scientists. The close integration of basic scientists and clinicians is integral to the success of the DZL and is facilitated by regular meetings, symposia, and access to common infrastructure. 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, CPC-M, TLRC, UGMLC
Number of Participating DZL Faculty	44

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 are rather uniform (e.g. 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 Disease Area Asthma and Allergy of the DZL.



Goals followed in 2014 – Asthma and Allergy

Goal 1 – German Collaborative Asthma Cohort

- Building an asthma and allergy patient registry, crossing the gap between pediatric and adult asthma
- Comprehensive clinical characterization of enrolled patients
- Collection of biomaterials for high throughput methods
- Integrating clinical and "omics" data by means of systems biology approaches
- Testing biomarkers in population-based cohorts

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. the role of granulocytes, T and B cells in pathogenesis) and pre-clinical studies
  - › Generation of Drosophila models for the functional characterization of novel candidate genes for asthma
  - › Establishment of an ex vivo model of an allergic immune response in human precision cut lung slices
- 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 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
  - › Human genome and epigenome analyses
  - › Comparative microbiome analysis in asthmatics from asthma cohort
  - › 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

Major Accomplishments Updated Through 2014

Collaborative Cohorts

» A patient registry (n=750) for future clinical trials has been established with identical comprehensive clinical tools across 3 pediatric DZL sites (ARCN, BREATH, CPC-M).
» A transition clinic from pediatric to adult asthma has been established at CPC-M and ARCN
» A comprehensive protocol for a clinical cohort for childhood (KIRA; n=293) and adult (ERA; n=116) new onset and established asthma has been set up with standardized instruments, SOPs and audits with site visits across several DZL sites (ARCN, BREATH, CPC-M). The program includes 'deep phenotyping', biosampling for analysis of allergic sensitization, immune responses, microbiome, virome and omics data, exacerbation visits, integrated data entry (WebSpirit) and advanced biostatistics.
» Close collaboration was established with the DA Cystic Fibrosis (shared questionnaires and biosampling protocols) and The German Center for Infection Research, DZIF (microbiome analysis).

Novel Techniques for Cellular and Molecular Phenotyping

» Establishment of primary human cell and tissue culture techniques including SOPs for induced sputum (Sewald & Braun, Xenobiotica 43:84, 2013)
» Set-up of asthma related transcriptomics (ARCN), miRNA expression profiling (ARCN, CPC-M, UGMLC), lipidomics (ARCN, UGMLC), surface proteomics (CPC-M) and chip-cytometry (BREATH) (Hennig et al, JACI 133:172, 2014*; Kaeuferle et al, Methods Mol Biol 1169:121, 2014*; Shevchuk et al, J Proteome Res 13:5230, 2014; Sittka et al, Adv Exp Med Biol 774:121, 2013).

Cellular Mechanisms of Asthma Development

» IL-31, induced by IL-4 and IL-33, amplifies an allergic TH2 inflammation via induction of inflammatory chemokines in bronchial epithelium (Stott et al, JACI 132:446, 2013).
» In Drosophila, Der p 1 activates components of the innate immune system including epithelial responses, suggesting that allergen-mediated proteolytic cleavage represents an ancient type of danger signaling (Warmbold et al, JI 190:366, 2013).
» In mice, DC expansion following pulmonary aeroallergen provocation is differentially regulated in airway mucosa versus parenchyma (Veres et al, JI 190:897, 2013).
» A cell surface protein expression atlas was established for naïve and activated CD4+ T cells by proteome technology (Graessel et al, Mol Cell Proteomics, 2015 May 19 [Epub ahead of print]).

Highlighted Publications, Lead by DZL Faculty – updated through 2014

Depner M, Fuchs O, Genuneit J, Karvonen AM, Hyvärinen A, Kaulek V, Roduit C, Weber J, Schaub B, Lauener R, Kabesch M, Pfefferle PI, Frey U, Pekkanen J, Dalphin JC, Riedler J, Braun-Fahrländer C, von Mutius E, Ege MJ; PASTURE Study Group. Clinical and epidemiologic phenotypes of childhood asthma. Am J Respir Crit Care Med 189:129, 2014 (BREATH, CPC-M, UGMLC)

Hennig C, Ilginus C, Boztug K, Skokowa J, Marodi L, Szaflarska A, Sass M, Pignata C, Kilic SS, Caragol I, Baumann U, Klein C, Welte K, Hansen G. High-content cytometry and transcriptomic biomarker profiling of human B-cell activation. J Allergy Clin Immunol 133:172, 2014 (BREATH)

Hagner S, Harb H, Zhao M, Stein K, Holst O, Ege MJ, Mayer M, Matthes J, Bauer J, von Mutius E, Renz H, Heine H, Pfefferle PI, Garn H. Farm-derived gram-positive bacterium Staphylococcus sciuri w620 prevents asthma phenotype in HDM- and OVA-exposed mice. Allergy 68:322, 2013 (ARCN, BREATH, CPC-M, UGMLC)

Stott B, Lavender P, Lehmann S, Pennino D, Durham S, Schmidt-Weber CB. Human IL-31 is induced by IL-4 and promotes TH2-driven inflammation. J Allergy Clin Immunol 132:446, 2013 (CPC-M)

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 129:1602, 2012 (UGMLC)

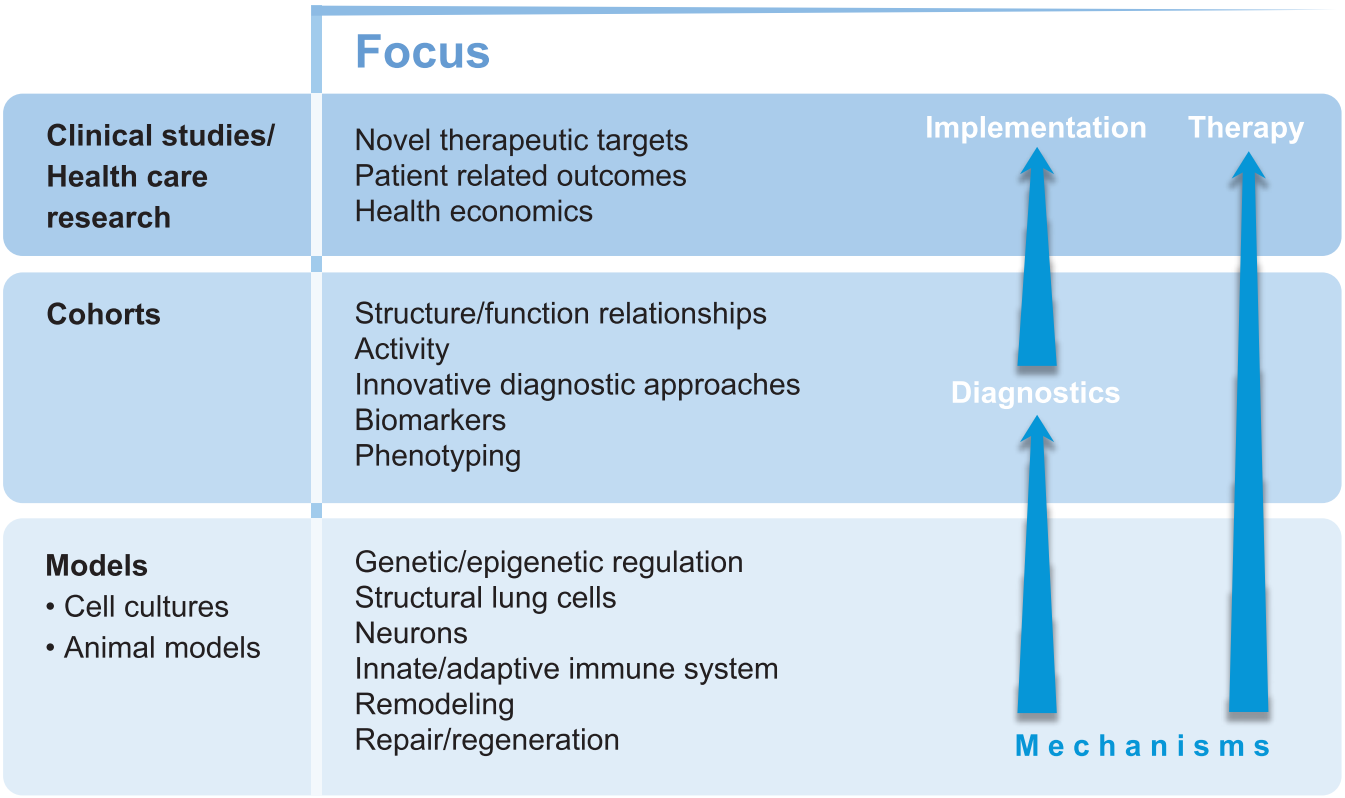
Fuchs O, Genuneit J, Latzin P, Büchele G, Horak E, Loss G, Sozanska B, Weber J, Boznanski A, Heederik D, Braun-Fahrländer C, Frey U, von Mutius E; GABRIELA Study Group. Farming environments and childhood atopy, wheeze, lung function, and exhaled nitric oxide. J Allergy Clin Immunol 130:382, 2012 (CPC-M)

Number of papers published by DZL Faculty in 2014 - Disease Area Asthma and Allergy: 96

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, CPC-M, TLRC, UGMLC
Number of Participating DZL Faculty	58

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 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 2014

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
- Identification of candidate genes through longitudinal phenotypic and molecular characterization of COPD mouse models
- Validation of candidate genes through genetic, functional, and pharmacological investigations in COPD mouse models
- 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
  - › Development of an algorithm for the diagnosis of COPD
  - › 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 in COPD patients by MRI
  - › MRI imaging in patients with COPD severity GOLD I - IV
- 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)
  - › Establishment of assays (FACS, microscopy) for FRET measurement in biosamples (sputum, BAL)
  - › Use of specific FRET sensors in patient samples for evaluation of proteolytic activity as a biomarker for pulmonary inflammation
- Functional Endpoints for COPD
  - › Functional measurements of ion transport (nasal potential difference) for the phenotypic characterization of COPD subtypes
- Mucins
  - › Development of mucin-reactive probes

Goal 3 – Measurement of physical activity

- › Longitudinal measurement of activity
- › Cross-sectional analyses
- › Analysis of longitudinal data

Goal 4 – Cohorts and clinical studies

- › Implementation of cohort studies
- › Clinical trials in cooperation with industry partners
- › Implementation of Investigator Initiated Trials after approval by the DZL "Clinical Trial Board"

Goal 5 – Healthcare Management and Healthcare Economics

- › Healthcare economic analysis of cost and quality of life with respect to COPD risk factors (e.g., smoking)
- › Data collection according to specific requests

Major Accomplishments Updated Through 2014

Novel Targets for COPD

» B cells (deficiency protects against COPD development) and immuno-aging increase susceptibility to cigarette smoke (CS)-induced COPD (John-Schuster et al, Am J Physiol Lung Cell Mol Physiol 307:L692, 2014)
» iNOS inhibition reverses CS-induced emphysema and PH in mice (>patent application); stimulation of soluble guanylate cyclase prevents CS-induced emphysema and PH (Seimetz et al, Cell 147:293, 2011; Weissmann et al, Am J Respir Crit Care Med 189:1359, 2014)
» Airway mucus obstruction triggers macrophage activation and matrix metalloproteinase 12-dependent emphysema (Trojanek et al, Am J Respir Cell Mol Biol 51: 709, 2014)

Novel Biomarkers

» Development and validation of FRET reporters for quantification of protease activity (NE and MMP12) in sputum and BAL (Trojanek et al, Am J Respir Cell Mol Biol 51: 709, 2014; Gehrig et al, Am J Respir Crit Care Med 189:1082, 2014; Gehrig et al, Angew Chem Int Ed 51:6258, 2012)
» CS-induced disruption of bronchial epithelial tight junctions is prevented by TGF-β (Schamberger et al, Am J Respir Cell Mol Biol 50:1040, 2014)
» Establishment of a novel VOC breath sampler for multicenter settings (BREATH, UGMLC)

Imaging

» Proof-of-concept for quantification of airway inflammation by MRI-T2 TIRM (Vogel-Claussen et al, Am J Respir Crit Care Med 189:650, 2014)
» Improved and early diagnosis of pulmonary emphysema using in vivo dark-field radiography (Schleede et al, PNAS 109:17880, 2012; Yaroschenko et al, Radiology 269:427, 2013; Meinel et al, Invest Radiol 49:653, 2014)
» Establishment of the COSYCONET Imaging Bank for the evaluation of the clinically indicated and collected retrospective CT data (TLRC)
» Successful start of the multi-center COSYCONET imaging subtrial using MRI and CT (all DZL sites)

Translation into Practice and Health Economics

» Design and development of the COPD BeoNet Registry as a comprehensive primary care database for economic and health care research to assess prevention, treatment and outcomes and their impact on quality of life and costs (BREATH, CPC-M, TLRC)
» Development and validation of a German model for cost-effectiveness evaluations of preventive and therapeutic COPD interventions (Menn et al, Pharmacoeconomics 30:825, 2012; Hoogendoorn et al, Value Health 17:525, 2014)
» Quality of life decline in early stage COPD patients remains small for several years leaving opportunity for prevention (Wacker et al, BMC Pulm Med 14:13, 2014)
» Official ERS statement on physical activity in COPD (Watz et al, Eur Resp J 44:1521, 2014)
» Interventional studies applying long-acting bronchodilators to improve physical activity in daily life in patients with COPD (Beeh et al, BMC Pulm Med 14:209, 2014, Watz et al, BMC Pulm Med 14: 158, 2014*)
» Establishment of CT for patient selection and planning tool of endoscopic lung volume reduction therapy (TLRC)

Highlighted Publications, Lead by DZL Faculty - updated through 2014

Albrecht E, [.....], Jörres RA, Heinrich J, Behr J, Huber RM, [.....], Schulz H. Telomere length in circulating leukocytes is associated with lung function and disease. Eur Resp J 43: 983, 2014 (CPC-M)

Gehrig S, Duerr J, Weitnauer M, Wagner CJ, Graeber SY, Schatterny J, Hirtz S, Belaaouaj A, Dalpke AH, Schultz C, Mall MA. Lack of neutrophil elastase reduces inflammation, mucus hypersecretion, and emphysema, but not mucus obstruction, in mice with cystic fibrosis-like lung disease. Am J Respir Crit Care Med 189:1082, 2014 (TLRC)

Rabe KF, Fabbri LM, Israel E, Kogler H, Riemann K, Schmidt H, Glaab T, Vogelmeier CF. Effect of ADRB2 polymorphisms on the efficacy of salmeterol and tiotropium in preventing COPD exacerbations: a prespecified substudy of the POET-COPD trial. Lancet Respir Med 2:44, 2014 (ARCN, UGMLC)

Schamberger AC, Mise N, Jia J, Genoyer E, Yildirim AÖ, Meiners S, Eickelberg O. Cigarette smoke-induced disruption of bronchial epithelial tight junctions is prevented by transforming growth factor-β. Am J Respir Cell Mol Biol 50:1040, 2014 (CPC-M)

Watz H, Barnacle H, Hartley BF, Chan R. Efficacy and safety of the p38 mapk inhibitor losmapimod for patients with chronic obstructive pulmonary disease: A randomised, double-blind, placebo-controlled trial. Lancet Respir Med 2:63, 2014 (ARCN)

Weissmann N, Lobo B, Pichl A, Parajuli N, Seimetz M, Puig-Pey R, Ferrer E, Peinado VI, Domínguez-Fandos D, Fysikopoulos A, Stasch JP, Ghofrani HA, Coll-Bonfill N, Frey R, Schermuly RT, García-Lucio J, Blanco I, Bednorz M, Tura-Ceide O, Tadele E, Brandes RP, Grimminger J, Klepetko W, Jaksch P, Rodriguez-Roisin R, Seeger W, Grimminger F, Barberà JA. Stimulation of soluble guanylate cyclase prevents cigarette smoke-induced pulmonary hypertension and emphysema. Am J Respir Crit Care Med 189:1359, 2014 (UGMLC)

Rabe KF, Fabbri LM, Vogelmeier C, Kogler H, Schmidt H, Beeh KM, Glaab T. Seasonal distribution of COPD exacerbations in the prevention of exacerbations with tiotropium in COPD trial. Chest 143:711, 2013 (ARCN, UGMLC)

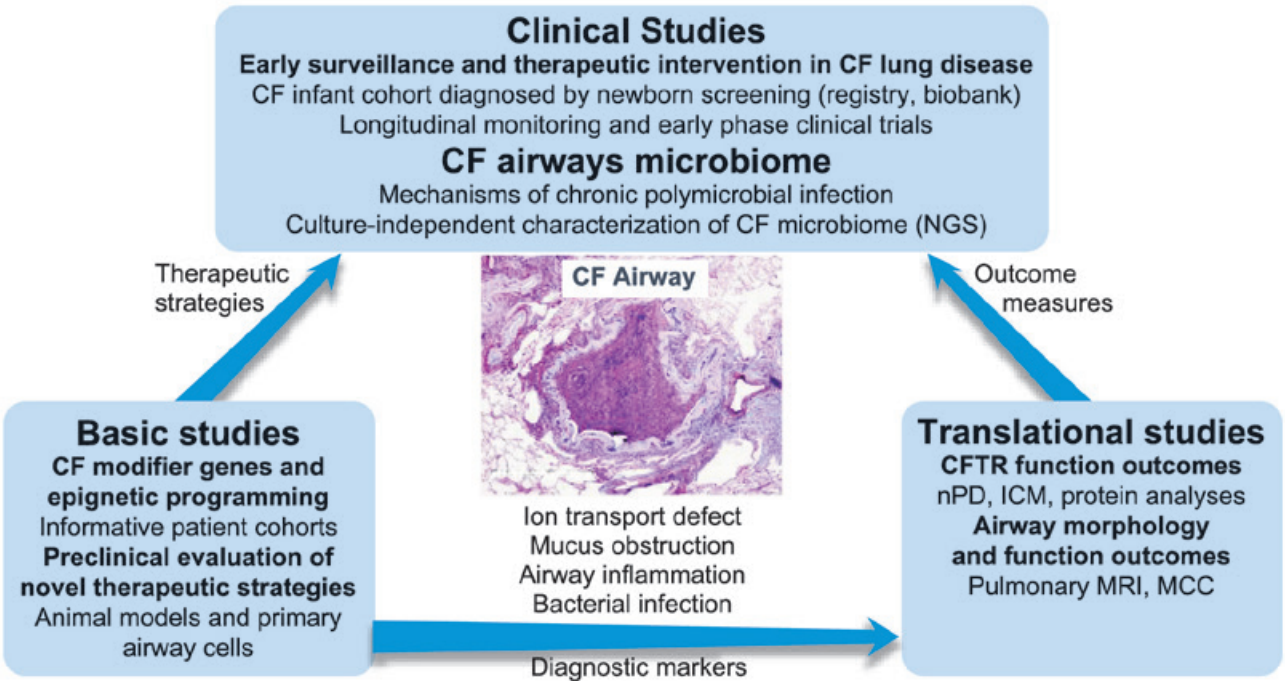
Röpcke S, Holz O, Lauer G, Müller M, Rittinghausen S, Ernst P, Lahu G, Elmlinger M, Krug N, Hohlfeld JM. Repeatability of and Relationship between Potential COPD Biomarkers in Bronchoalveolar Lavage, Bronchial Biopsies, Serum, and Induced Sputum. PLoS One 7:e46207, 2012 (BREATH)

Number of papers published by DZL Faculty in 2014 – Disease Area COPD: 90

Cystic Fibrosis

Disease Area Leaders	Prof. Dr. Marcus Mall (TLRC)
	Prof. Dr. Dr. Burkhard Tümmler (BREATH)
Participating DZL Partner Sites	ARCN, BREATH, TLRC, UGMLC
Number of Participating DZL Faculty	21

Cystic fibrosis (CF) is the most common genetically determined, early onset and still lethal form of chronic obstructive lung disease. CF affects approximately one in 2500 newborns in Caucasian populations. With improvements in symptomatic therapies and standardized CF medical care, the median survival of CF patients in Germany has increased to approximately 40 years of age. However, despite recent breakthroughs in disease-modifying therapies for a small subgroup of patients with specific CF genotypes, there are currently no therapies available that target CF lung disease at its root cause in the majority of patients. 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.



Disease Area Cystic Fibrosis Research Strategy

Goals Followed in 2014 – 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 CF sibling pairs
  - › Replication study to confirm disease modifying genes in the German CF cohort
  - › Identification of disease modifying genes in a mouse model of CF lung disease
  - › Functional validation of chosen candidate genes and identification of new therapeutic strategies in transgenic mouse models
- Epigenetic Programming of CF Lung Disease
  - › Sequencing of immunoglobulin and T-cell receptor genes in monozygotic (identical) twins with CF
  - › Methylation analysis to evaluate epigenetic changes in monozygotic twins with CF
- Preclinical evaluation of mucolytic and anti-inflammatory treatment strategies
  - › Preclinical evaluation of DNAzymes to correct the ion transport defect in β ENaC overexpressing mice
  - › Preclinical evaluation of new anti-inflammatory strategies 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 the CFTR analysis (nPD, ICM and CFTR immunoblots) to improve CF diagnosis
  - › Evaluation and use of CFTR analysis (ICM CFTR and immunoblot) for ex vivo testing of novel CFTR modulators
- 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
  - › Comparison of the disease process in early diagnosed CF patients from the newborn screening cohort and clinically diagnosed CF patients with intensified conventional therapy
  - › Conducting a Phase 2a study for preventive treatment 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

Major Accomplishments Updated Through 2014

Clinical trial:

» established first multicenter Phase 2 study on preventive inhalation of hypertonic saline (PRESIS) in CF infants diagnosed by newborn screening (NCT01619657).

Cohort studies:

» implementation of CF newborn screening (Sommerburg et al, J Cyst Fibros 13:15, 2014) and establishment of CF infant cohort (TRACK-CF) for observational studies of early lung disease (NCT02270476).

CF microbiome:

» elucidation of microbiome structure, host and pathogen factors (Moura-Alves et al, Nature 512:387, 2014; Pewzner-Jung et al, EMBO Mol Med 6:1209, 2014) and technological advances in metagenomics (Davenport & Tümmler, Environ Microbiol 15:1, 2013).

Novel quantitative outcome measures:

» Implementation of magnetic resonance imaging (MRI) and multiple breath washout (MBW) as non-invasive outcome measures of lung structure and function (Eichinger et al Eur J Radiol 81:1321, 2012; Wielpütz et al, AJRCCM 189:956, 2014; Stahl et al, Respiration 87:357, 2014) and intestinal current measurements (ICM) as sensitive measure of functional rescue of mutant CFTR by emerging CFTR modulators (Roth et al, PLOS ONE 6:e24445, 2011; van Barneveld et al, Cell Physiol Biochem 30:587, 2012; Beekman et al, J Cyst Fibros 13:363, 2014).

Preclinical evaluation of novel therapeutic strategies:

» proof-of-concept that novel long acting sodium channel blockers and hypertonic saline are effective in prevention of CF-like airways mucus obstruction in mice (Graeber et al, AJRCMB 49:410, 2013; Mall et al Int J Biochem Cell Biol 52:174, 2014). Contribution to bronchoalveolar sublineage specification of pluripotent stem cells (Schmeckebier et al, Tissue Eng Part A 19:938, 2013).

Highlighted Publications, Lead by DZL Faculty - updated through 2014

Gehrig S, Duerr J, Weitnauer M, Wagner CJ, Graeber SY, Schatterny J, Hirtz S, BelaaouaJ A, Dalpke AH, Schultz C, Mall MA. Lack of neutrophil elastase reduces inflammation, mucus hypersecretion, and emphysema, but not mucus obstruction, in mice with cystic fibrosis-like lung disease. Am J Respir Crit Care Med 189:1082, 2014 (TLRC)

Stanke F, van Barneveld A, Hedtfeld S, Wölfl S, Becker T, Tümmler B. The CF-modifying gene EHF promotes p.Phe508del-CFTR residual function by altering protein glycosylation and trafficking in epithelial cells. Eur J Hum Genet 22:660, 2014 (BREATH)

Wielpütz MO, Puderbach M, Kopp-Schneider A, Stahl M, Fritzsching E, Sommerburg O, Ley S, Sumkauskaite M, Biederer J, Kauczor HU, Eichinger M, Mall MA. Magnetic resonance imaging detects changes in structure and perfusion, and response to therapy in early cystic fibrosis lung disease. Am J Respir Crit Care Med 189:956, 2014 (TLRC)

Graeber SY, Zhou-Suckow Z, Schatterny J, Hirtz S, Boucher RC, Mall MA. Hypertonic saline is effective in the prevention and treatment of mucus obstruction, but not airway inflammation, in mice with chronic obstructive lung disease. Am J Respir Cell Mol Biol 49:410, 2013 (TLRC)

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 122:3629, 2012 (TLRC, BREATH)

Gehrig S, Mall MA, Schultz C. Spatially resolved monitoring of neutrophil elastase activity with ratiometric fluorescent reporters. Angew Chem Int Ed Engl 51:6258, 2012 (TLRC)

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 302:69, 2012 (BREATH)

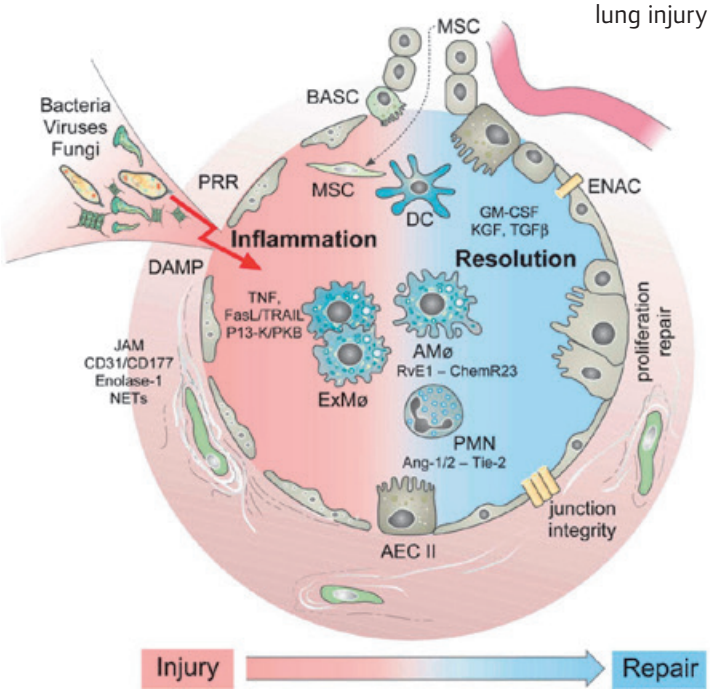
Number of papers published by DZL Faculty in 2014 - Disease Area CF: 41

Pneumonia and Acute Lung Injury

Disease Area Leaders	Prof. Dr. Jürgen Lohmeyer (UGMLC)
	Prof. Dr. Tobias Welte (BREATH)
Participating DZL Partner Sites	ARCN, BREATH, CPC-M, TLRC, UGMLC
Number of Participating DZL Faculty	27

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, acute respiratory distress syndrome (ARDS), and an unacceptably high mortality rate, underscore an urgent medical need for novel, effective therapeutic approaches.

Both microbial attack (bacteria, viruses, fungi) and non-microbial inflammatory injury (aspiration, toxic gases) may cause acute lung injury with severe respiratory failure. The goals of this Disease Area are to dissect the molecular mechanisms underlying the spread 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 targeted therapeutic concepts are being developed to attenuate lung injury in pneumonia and ARDS.



(AEC II – alveolar type II cells; AMø – alveolar macrophage; Ang – angiopoietin; BASC – bronchioalveolar stem cells; DAMP – damage-associated molecular patterns; DC – dendritic cell; ENAC – epithelial sodium 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 2014 – 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
  - › Identification of "Immune Escape" strategies of pulmonary pathogens
  - › Evaluation of the role of "Brush cells" as sensors of microbial pathogens in the bronchial tree
- Translational Research
  - › Analysis of pulmonary host defense in WT and C-type Lectin (CLR) deficient mice with sepsis
  - › Investigation of the importance of CLR blockade by function-blocking antibodies for the course and severity of pneumococcal pneumonia
  - › Preclinical evaluation of further pulmonary pattern recognition molecules as potential targets for therapeutic intervention
- 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
  - › Analysis of conditional mutant mice with lung cell type specific gene targeting
- Translational Research
  - › Analysis of effector cell function resident macrophages in the presence and absence of overexpressed pulmonary cytokines
  - › Evaluation of protective immunity of the lung against S. pneumoniae through lung specific overexpression of relevant chemokines
- Clinical Research
  - › Evaluation of molecular inflammatory signatures for individualized pneumonia / ARDS therapy

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
  - › Purification and molecular genetic characterization of DC subsets with respect to inflammatory candidate genes relevant to pulmonary barrier dysfunction in the course of pneumococcal pneumonia
  - › Analysis of anti-inflammatory, pro-resolution and alveolar repair mediating capacity of mesenchymal stem cells
- Clinical Research
  - › Conduct a clinical MSC pilot study in patients with refractory ARDS

Goal 4 – Preventive Strategies

- Evaluation of pneumococcal protein-based immunization in pneumococcal colonization invasion model
- Validation of the role of basophil function in strengthening the secondary immune response to pneumococcal protein antigens in the mouse
- Establishment of cell culture systems for the characterization of human basophils against S. pneumonia

Major Accomplishments Updated Through 2014

» Identification of a novel microbe sensing mechanism by taste receptors (Krasteva et al, Proc Natl Acad Sci U S A 108:9478, 2011; Krasteva et al, Life Sci 91:992, 2012); identification of pneumococcal glycolipid binding to Mincle triggering protective Syk-Card9-dependent responses (unpublished); characterization of NLRP3-inflammasome activation by non-typeable Haemophilus influenzae (Rotta Detto Loria et al, PLoS One 8:e66818, 2013) and dissection of functional plasticity of alveolar recruited exudate macrophages in pneumonia models (Herold et al, AJRCCM 183:1380, 2011)

» Characterization of C-Jun-N-terminal kinase in CO2-induced epithelial dysfunction and of megalin/GSK3-β in trans-epithelial albumin clearance (Vadász et al, PLoS One 7:e46696, 2012; Buchäckert et al, J Physiol 590:5167, 2012); characterization of TGF-β directed ENaC trafficking in ion/fluid transport in ALI (Peters et al, Proc Natl Acad Sci U S A 111:E374, 2014); characterization of AEC Na,K-ATPase expression/localization in IAV infection (unpublished) and of membrane insertion of ENaC in alveolar epithelium in hypoxia (unpublished) as novel targets to treat barrier failure

» Discovery of a new mechanism of alveolar damage in ALI mediated by histones of neutrophil extracellular traps (NETs) (Saffarzadeh et al, PLoS One 7:e32366 2012) and of new targets for tissue protection such as agonistic anti-TRAIL receptor DR5 directed antibody treatment (Steinwede et al, J Exp Med 209:1937 2012) and locally released/delivered GM-CSF in pneumonia models (Steinwede et al, J Immunol 187:5346, 2011; Unkel et al, J Clin Invest 122:3652, 2012)

» Discovery of Fgf10/Fgfr2b-driven epithelial repair from a distal airway progenitor pool in influenza A pneumonia (El Agha et al, Development 141:296, 2014; unpublished)

» Development of a novel basophil-dependent pneumococcal protein-based vaccination strategy against S. pneumoniae (Bischof et al, J Infect Dis 210:14, 2014) and establishment of nasopharyngeal colonization models with S. pneumoniae in mice (unpublished)

» GMP practice-compliant animal-free expansion of human bone marrow derived mesenchymal stem cells (Nold et al, Biochem Biophys Res Commun 430:325, 2013; Nold et al, Cytotherapy 17:152, 2014)

» Immunomodulation by lipid emulsions in pulmonary inflammation (Hecker et al, Crit Care, in press)

» Establishment of new registries: PROGNOSIS; Continuation of established cohort studies (CAPNETZ, PROGRESS) with DZL support; Participation in EU funded international registries for emerging infections (PREPARE, de Jong et al, Euro Surveill 19:20980, 2014) and non CF bronchiectasis (EMBARC); Participation in IMI funded project about bacterial resistance (COMBACTE) and the development of inhaled antibiotics for bronchiectasis (CF and non CF, iABC)

» Initiation of clinical studies: inhaled GM-CSF as treatment of pneumonia-associated ARDS (compassionate use; phase II GI-Hope Study) (Herold et al, Am J Respir Crit Care Med 189:609, 2014; EudraCT-No.: 2014-002479-28

Highlighted Publications, Lead by DZL Faculty - updated through 2014

Herold S, Hoegner K, Vadasz I, Gessler T, Wilhelm J, Mayer K, Morty RE, Walmrath HD, Seeger W, Lohmeyer J. Inhaled granulocyte/macrophage colony-stimulating factor as treatment of pneumonia-associated acute respiratory distress syndrome. Am J Respir Crit Care Med 189:609, 2014 (UGMLC)

Peters DM, Vadasz I, Wujak L, Wygrecka M, Olschewski A, Becker C, Herold S, Papp R, Mayer K, Rummel S, Brandes RP, Gunther A, Waldegger S, Eickelberg O, Seeger W, Morty RE. TGF-beta directs trafficking of the epithelial sodium channel ENaC which has implications for ion and fluid transport in acute lung injury. Proc Natl Acad Sci U S A 111:374, 2014 (UGMLC, CPC-M)

Hogner K, Wolff T, Pleschka S, Plog S, Gruber AD, Kalinke U, Walmrath HD, Bodner J, Gattenlohner S, Lewe-Schlosser P, Matrosovich M, Seeger W, Lohmeyer J, Herold S. Macrophage-expressed IFN-beta contributes to apoptotic alveolar epithelial cell injury in severe influenza virus pneumonia. PLoS Pathog 9:e1003188, 2013 (UGMLC)

Brunkhorst FM, Oppert M, Marx G, Bloos F, Ludewig K, Putensen C, Nierhaus A, Jaschinski U, Meier-Hellmann A, Weyland A, Gründling M, Moerer O, Riessen R, Seibel A, Ragaller M, Büchler MW, John S, Bach F, Spies C, Reill L, Fritz H, Kiehntopf M, Kuhnt E, Bogatsch H, Engel C, Loeffler M, Kollef MH, Reinhart K, Welte T; German Study Group Competence Network Sepsis (SepNet). Effect of empirical treatment with moxifloxacin and meropenem vs meropenem on sepsis-related organ dysfunction in patients with severe sepsis: a randomized trial. JAMA 307:2390-9, 2012 (BREATH)

Lepper PM, Ott S, Nüesch E, von Eynatten M, Schumann C, Pletz MW, Mealing NM, Welte T, Bauer TT, Suttorp N, Jüni P, Bals R, Rohde G; German Community Acquired Pneumonia Competence Network. Serum glucose levels for predicting death in patients admitted to hospital for community acquired pneumonia: prospective cohort study. BMJ 344:e3397, 2012 (BREATH)

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, 2012 (BREATH)

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 122(10):3652, 2012 (UGMLC)

Weber M, Lambeck S, Ding N, Henken S, Kohl M, Deigner HP, Enot DP, Igwe EI, Frappart L, Kiehntopf M, Claus RA, Kamradt T, Weih D, Vodovotz Y, Briles DE, Ogunniyi AD, Paton JC, Maus UA*, Bauer M*. Hepatic induction of cholesterol biosynthesis reflects a remote adaptive response to pneumococcal pneumonia. FASEB J 26(6):2424, 2012 (BREATH) *denotes shared senior authorship

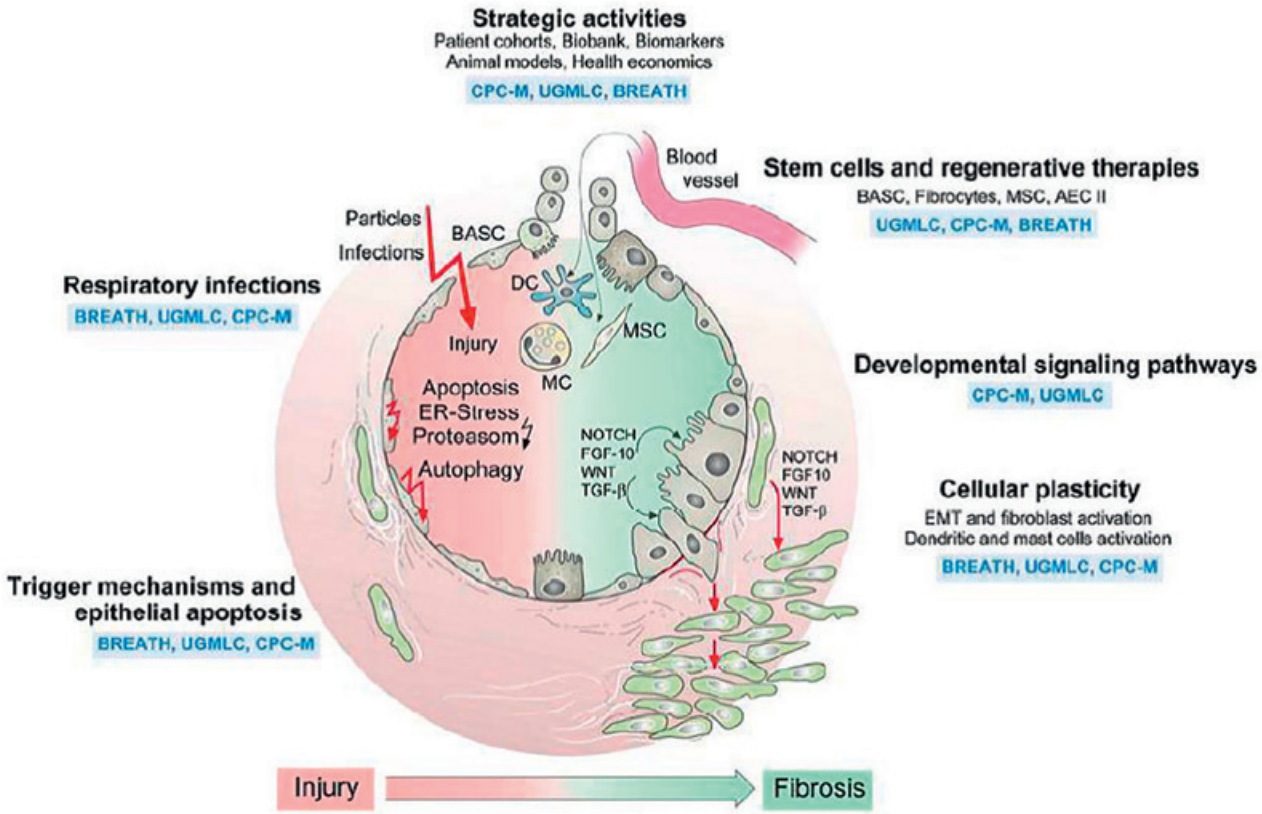
Herold S, Tabar TS, Janssen H, Hoegner K, Cabanski M, Lewe-Schlosser P, Albrecht J, Driever F, Vadasz I, Seeger W, Steinmueller M, Lohmeyer J. Exudate macrophages attenuate lung injury by the release of IL-1 receptor antagonist in gram-negative pneumonia. Am J Respir Crit Care Med 183:1380-90, 2011 (UGMLC)

Number of papers published by DZL Faculty in 2014 - Disease Area ALI: 40

Diffuse Parenchymal Lung Disease (DPLD)

Disease Area Leaders	Prof. Dr. Oliver Eickelberg (CPC-M)
	Prof. Dr. Andreas Günther (UGMLC)
Participating DZL Partner Sites	BREATH, CPC-M, TLRC, UGMLC
Number of Participating DZL Faculty	30

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 patients 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 paradigms 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.



(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 2014 – 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 proteasome function for ER-stress induced apoptosis in IPF
- Elucidation of the subcellular distribution and binding partners of Hermansky-Pudlak Syndrome gene products
- 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
- Evaluation and standardization of Wnt-inducible signaling protein-1 bioassays as a diagnostic biomarker for DPLD
- 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
- Definition of an immune cell-mediated therapeutic approach for attenuating pulmonary fibrosis in animal models
- 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

- Impact of Gram +/ - bacteria on onset and progression of pulmonary fibrosis
- Elucidation of the influence of pulmonary fibrosis on the clearance of pathogens from the lungs
- Description of the microbiomes of IPF patients
- Conduct a clinical study on the efficacy of clarithromycin treatment for the prevention of respiratory infections and thus the progression of IPF

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

Major Accomplishments Updated Through 2014

» **Establishment of DLPD registries and guidelines; progress in early diagnosis:** Management of patients with idiopathic pulmonary fibrosis in clinical practice: the INSIGHTS-IPF registry (Behr J et al. BMJ Open Respir Res 1:e000010, 2014), CT Diagnosis of IPF/ DPLD w/o honeycombing (Raghu et al. Lancet Resp Med, 2:277, 2014), International and German Guidelines for IPF (Travis et al. Am J Respir Crit Care Med 188: 733, 2013; Behr et al. Pneumologie 67:81, 2013)

» **Therapeutic responses in IPF:** Identification of individual treatment responses to pirfenidone (Loeh et al. Am J Respir Crit Care Med 191:110, 2015), lack of efficacy of macitentan in IPF (Raghu et al. Eur Resp J 42:1622, 2013)

» **Systemic deep phenotyping (tissue and BALF) in lung fibrosis:** proteomic characterization of IPF lung tissue (Korfei et al. J Proteomics. 85:109, 2013, Korfei et al. J Proteome Res. 10:2185 2011), CCL18 as biomarker for systemic sclerosis (Schupp et al. Eur Resp J 43:1530 2014)

» **Identification of novel drug targets in IPF:** WNT/ WISP1 and FGF signaling, NO/DDAH metabolism (Aumiller et al. Am J Respir Cell Mol Biol 49:96, 2013; Berschneider et al. Int J Biochem Cell Biol 53:432, 2014; Melboucy-Belkhir et al. Am J Physiol Lung Cell Mol Physiol 307:L838, 2014; Conte et al. Lab Invest. 93:566, 2013; Nkyimbeng T et al. PLoS One 8:e73279, 2013; Pullamsetti et al. Sci Transl Med 3:87ra53, 2011), coagulation cascade (Wygrecka M et al. Am J Respir Crit Care Med. 183:1703, 2011; Wygrecka M et al. Am J Respir Crit Care Med. 184:438 2011)

» **Extracellular matrix remodelling in neonatal CLD** (Hilgendorff et al. Am J Respir Cell Mol Biol. 50:233, 2014)

» **Developmental Signaling in DPLD** (Baarsma et al. Pharmacol Ther. 138:66 2013; Berschneider et al. Int J Biochem Cell Biol 53:432, 2014; Aumiller et al. Am J Respir Cell Mol Biol Jul;49:96, 2013)

» **Alveolar epithelial cell reprogramming in DPLD:** altered surfactant and ATII cell stress in fibrosis (Mahavadi P et al. Toxicol Sci. 142:285 2014)

» **Proteasome dysfunction in IPF** (Meiners et al. Antioxid Redox Signal 21:2364, 2014)

» **Novel methods for drug application, delivery and detection:** Patented method of lung epithelial cell drug application in vitro (Lenz et al. Am J Respir Cell Mol Biol 51:526, 2014), nano-particle-mediated drug delivery to lung epithelium (van Rijt et al., Eur Respir J 44:765, 2014), detection of pirfenidone metabolites in the fibrotic lung (Huber et al. Histochem Cell Biol 142:361, 2014)

» **Complex phenotypic tissue and stem cell assays:** Novel 3D fibroblast invasion assays (Burgstaller et al. PLoS One. 8:e63121, 2013), analysis of induced pluripotent stem cells (Tang et al. Methods Mol Biol 1029:17, 2013; Drukker et al. Nat Biotechnol. 30:531 2012; Tang et al. Nat Biotechnol.29:829, 2011)

» **Pulmonary x-ray diagnosis:** Novel preclinical small-animal X-ray dark-field scanner in neonatal and adult mice (Schleede et al. Proc Natl Acad Sci U S A. 109:17880, 2012; Yaroshenko et al. Radiology 269:427 2013)

Highlighted Publications, Lead by DZL Faculty - updated through 2014

Schupp J, Becker M, Günther J, Müller-Quernheim J, Riemekasten G, Prasse A. Serum CCL18 is predictive for lung disease progression and mortality in systemic sclerosis. Eur Respir J 43:1530, 2014 (BREATH)

Aumiller V, Balsara N, Wilhelm J, Günther A, Königshoff M. WNT/β-catenin signaling induces IL-1β expression by alveolar epithelial cells in pulmonary fibrosis. Am J Respir Cell Mol Biol. 49:96, 2013 (CPC-M, UGMLC)

Fernandez IE, Eickelberg O. New cellular and molecular mechanisms of lung injury and fibrosis in idiopathic pulmonary fibrosis. Lancet 380:680, 2012 (DPLD)

Hilgendorff A, Parai K, Ertsey R, Jain N, Navarro EF, Peterson JL, Tamosiuniene R, Nicolls MR, Starcher BC, Rabinovitch M, Bland RD. Inhibiting lung elastase activity enables lung growth in mechanically ventilated newborn mice. Am J Respir Crit Care Med 184:537, 2011 (CPC-M)

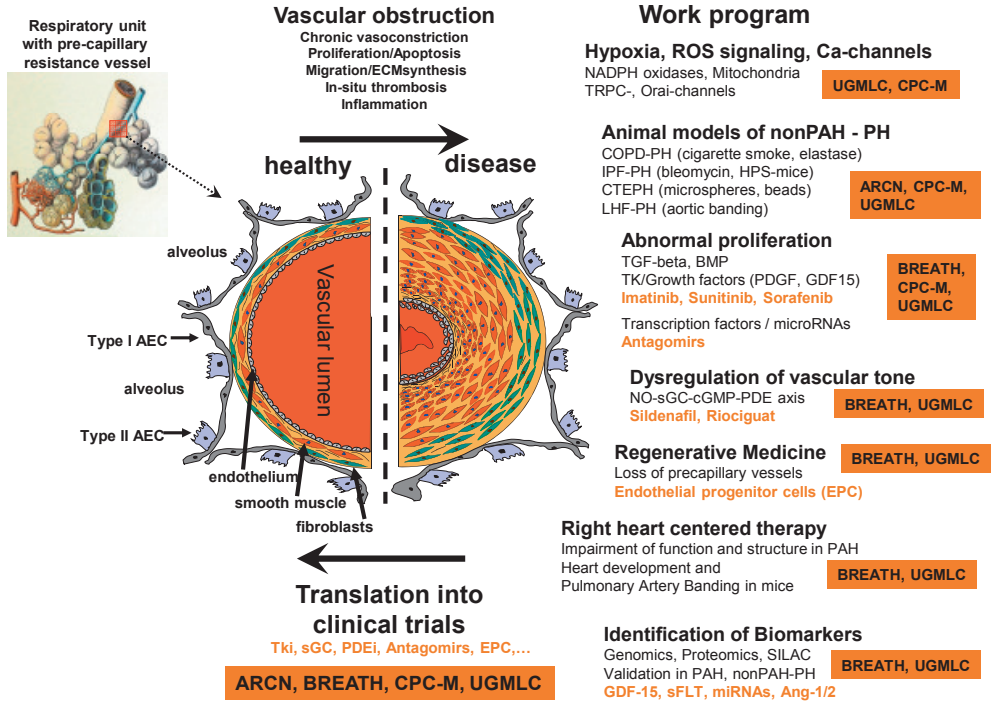
Pullamsetti SS, Savai R, Dumitrascu R, Dahal BK, Wilhelm J, Konigshoff M, Zakrzewicz D, Ghofrani HA, Weissmann N, Eickelberg O, Guenther A, Leiper J, Seeger W, Grimminger F, Schermuly RT. The role of dimethylarginine dimethylaminohydrolase in idiopathic pulmonary fibrosis. Sci Transl Med 3:87ra53, 2011 (CPC-M, UGMLC)

Number of papers published by DZL Faculty in 2014 – Disease Area DPLD: 30

Pulmonary Hypertension

DiseDisease Area Leaders	Prof. Dr. H. Ardeschir Ghofrani (UGMLC)
	Prof. Dr. Ralph T. Schermuly (UGMLC)
Participating DZL Partner Sites	ARCN, BREATH, CPC-M, TLRC, UGMLC
Number of Participating DZL Faculty	29

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-beta, transforming growth factor beta; 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 2014 – Pulmonary Hypertension

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

- Hypoxia, ROS signaling pathways and hypoxia-induced gene regulation in PH
  - › Generation of transgenic mice with reactive oxygen species (ROS) sensitive fluorescent proteins
  - › 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
  - › Examination of the role of HIF by the use of transgenic mice (prolyl hydroxylase (PHD) and Siah ubiquitin ligase)
- New calcium (Ca2 +) influx pathways 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
  - › Identification of new genes regulated by TRP or Orai channels through use of genomic and proteomic techniques
- 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
  - › Testing of new and approved compounds for treatment of PAH in animal models of DPLD
  - › Establishment of a model for CTEPH (pulmonary embolism by injection of microparticles) to study PH, and for testing of new and approved compounds for treatment of PAH

Goal 2 – Translational Research

- Promotion of vascular remodeling in PH: transcription factors and receptor tyrosine kinases
  - › Generation and characterization of a novel transgenic mouse (conditional PDGFR-β knockout mouse)
  - › Identification of growth factor receptors as potential biomarkers for monitoring treatment in human circulating monocytes
- Reverse remodeling by NO-guanylate cyclase-phosphodiesterase-axis
  - › Development of inhaled therapy strategies (e.g., nanoparticles)
  - › 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
  - › Identification of promising drug targets and testing their antiproliferative capacity by antagomir treatment in vitro and in preclinical animal models
  - › Identification of circulating miRNAs as potential biomarkers for the assessment of disease severity and treatment success
- Endothelial progenitor cell (EPC)-based revascularization of the lung
  - › Isolation of EPCs in from human peripheral blood; manipulation of these cells by pharmacological approaches and transfection technology
  - › Testing the efficacy of EPCs in preclinical animal models of PH for possible "reverse remodeling" potential
- Treatment of PH with a focus on the right heart
  - › Investigation of the effect of compounds approved for PAH on right ventricular function and structure in the pulmonary arterial banding model

Goal 3 – Clinical Research

- Non-hypothesis-based screen for new biomarkers
  - › Examination of tissue from patients with PAH or non-PAH PH compared to healthy individuals
  - › Implementation of broad genome, transcriptome and epigenomanalyse screens in lung tissue and in selected compartments of the lung
  - › 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
- Early clinical studies
  - › Conducting studies of sildenafil in ILD-PH: Long-term treatment (3 months) of ILD-PH patients with sildenafil
  - › Conducting studies of sildenafil and statin in COPD PH: long-term treatment (6 months) in patients with COPD and "out-of-proportion" -PH (COPD-PH) with sildenafil, and simvastatin

Major Accomplishments Updated Through 2014

» Worldwide approval of Riociguat and Macitentan for different forms of PH (EMA and FDA, 2014)

» Efficacy of the soluble guanylate cyclase stimulator Riociguat was demonstrated in PAH (Ghofrani et al, N Engl J Med 369:330, 2013) and CTEPH (Ghofrani et al, N Engl J Med 369:319, 2013) in phase 3 trials

» Efficacy of the endothelin antagonist Macitentan (Pulido et al, N Engl J Med 369:809, 2013) and the tyrosine kinase inhibitor Imatinib (Hoeper et al, Circulation 127:1128, 2013) was demonstrated in PAH in phase 3 trials

» Generation of the large scaled database COMPERA (Hoeper et al, Int J Cardiol 168:871, 2013, Olsson et al, Circulation 129:57, 2014) and identification of novel biomarkers (Rhodes et al, Am J Respir Crit Care Med 187:294, 2013; Becker et al, Am J Respir Crit Care Med 190:808, 2014; Kuempers et al, Eur Heart J 31:2291, 2010; Lorenzen et al, Chest 139:1010, 2011; Nickel et al, Respir Res 14:130, 2013)

» Development and refinement of tailored anti-remodeling and reverse-remodeling strategies (Lang et al, PLoS One 7:e43433, 2012; Kojonazarov et al, Int J Cardiol 167:2630, 2013; Savai et al, Nat Med 20:1289, 2014; Weissmann et al, Am J Respir Crit Care Med 189:1359, 2014; Weisel et al, Circulation 129:1510, 2014)

» Identification and characterization of TRPC channels (Weissmann et al, Nat Commun 3:649, 2012, Malczyk et al, Am J Respir Crit Care Med 188:1451, 2013), sources of reactive oxygen species (Veit et al, Antioxid Redox Signal 19:2213, 2013), FoxO transcription factors (Savai et al, Nat Med 20:1289, 2014), and receptor tyrosine kinases (Kwapiszewska et al, Am J Pathol 181:2018, 2012; Novoyatleva et al, FASEB J 28:2492, 2014) as novel targets for treatment of PH

Highlighted Publications, Lead by DZL Faculty - updated through 2014

Olsson KM, Delcroix M, Ghofrani HA, Tiede H, Huscher D, Speich R, Grünig E, Staehler G, Rosenkranz S, Halank M, Held M, Lange TJ, Behr J, Klose H, Claussen M, Ewert R, Opitz CF, Vizza CD, Scelsi L, Vonk-Noordegraaf A, Kaemmerer H, Gibbs JS, Coghlan G, Pepke-Zaba J, Schulz U, Gorenflo M, Pittrow D, Hoeper MM. Anticoagulation and survival in pulmonary arterial hypertension: results from the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA). Circulation 129:57, 2014 (BREATH, CPC-M, TLRC, UGMLC)

Savai R, Al-Tamari HM, Sedding D, Kojonazarov B, Muecke C, Teske R, Capecchi MR, Weissmann N, Grimminger F, Seeger W, Schermuly RT, Pullamsetti SS. Pro-proliferative and inflammatory signaling converge on FoxO1 transcription factor in pulmonary hypertension. Nat Med 20:1289, 2014 (UGMLC)

Ghofrani HA, D'Armini AM, Grimminger F, Hoeper MM, Jansa P, Kim NH, Mayer E, Simonneau G, Wilkins MR, Fritsch A, Neuser D, Weimann G, Wang C; CHEST-1 Study Group. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. N Engl J Med. 369:319, 2013 (BREATH, UGMLC)

Ghofrani HA, Galiè N, Grimminger F, Grünig E, Humbert M, Jing ZC, Keogh AM, Langleben D, Kilama MO, Fritsch A, Neuser D, Rubin LJ; PATENT-1 Study Group. Riociguat for the treatment of pulmonary arterial hypertension. N Engl J Med 369:330, 2013 (TLRC, UGMLC)

Hoeper MM, Barst RJ, Bourge RC, Feldman J, Frost AE, Galié N, Gómez-Sánchez MA, Grimminger F, Grünig E, Hassoun PM, Morrell NW, Peacock AJ, Satoh T, Simonneau G, Tapson VF, Torres F, Lawrence D, Quinn DA, Ghofrani HA. Imatinib mesylate as add-on therapy for pulmonary arterial hypertension: results of the randomized IMPRES study. Circulation 127:1128, 2013 (BREATH, TLRC, UGMLC)

Malczyk M, Veith C, Fuchs B, Hofmann K, Storch U, Schermuly RT, Witzenrath M, Ahlbrecht K, Fecher-Trost C, Flockerzi V, Ghofrani HA, Grimminger F, Seeger W, Gudermann T, Dietrich A, Weissmann N. Classical transient receptor potential channel 1 in hypoxia-induced pulmonary hypertension. Am J Respir Crit Care Med 188:1451, 2013 (CPC-M, UGMLC)

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 185: 409, 2012 (UGMLC)

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 186:897, 2012 (UGMLC)

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 3:649, 2012 (CPC-M, UGMLC)

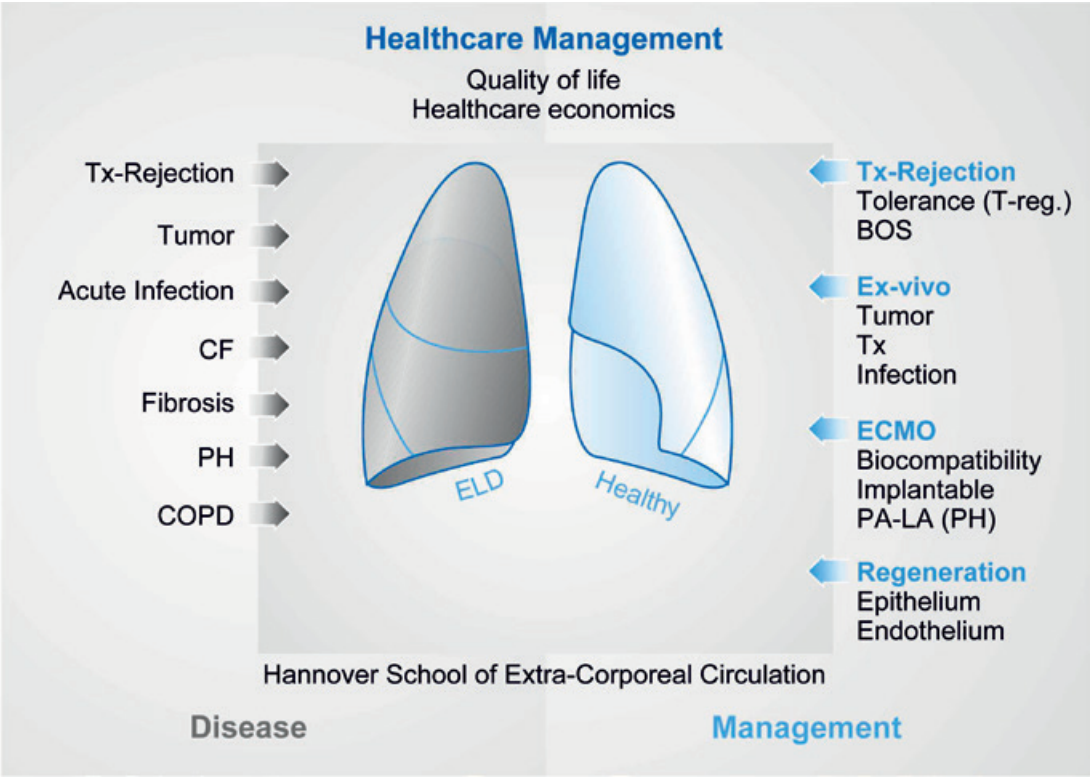
Seimetz M, Parajuli N, Pichl A, Veit F, Kwapiszewska G, Weisel FC, Milger K, Egemnazarov B, Turowska A, Fuchs B, Nikam S, Roth M, Sydykov A, Medebach T, Klepetko W, Jaksch P, Dumitrascu R, Garn H, Voswinckel R, Kostin S, Seeger W, Schermuly RT, Grimminger F, Ghofrani HA, Weissmann N. Inducible NOS inhibition reverses tobacco-smoke-induced emphysema and pulmonary hypertension in mice. Cell 147:293, 2011 (UGMLC)

Number of papers published by DZL Faculty in 2014 - Disease Area PH: 68

End-Stage Lung Disease

Disease Area Leaders	Prof. Dr. Dr. Axel Haverich (BREATH)
	Prof. Dr. Veronika Grau (UGMLC)
Participating DZL Partner Sites	BREATH, CPC-M, UGMLC
Number of Participating DZL Faculty	33

Various acute and chronic lung disorders ultimately lead to end-stage lung disease (ELD). Once all options for mechanical ventilation have been exhausted, only two treatment options remain for these patients on the brink of death: extracorporeal lung oxygenation (ECMO) and lung transplantation (LTx) Today ECMO therapy remains restricted to short-term application, primarily as a bridge to transplantation and as a 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 can be severely compromised by chronic rejection. Regenerative therapies that promote endogenous repair, cell transplantation, or tissue engineering are currently not available. The DZL ELD program aims to refine transplantation procedures and to minimize acute and chronic rejection. It also aims to optimize ECMO therapy towards fully implantable devices and set the stage for regeneration of diseased lung tissue. These aims are being tackled by stem-cell researchers, bioengineers, and first line clinicians and surgeons using a multi-faceted approach.



Goals Followed in 2014 – End-stage Lung Disease

Goal 1 – Lung Transplantation

- Immunology in Lung Transplantation
  - › Immunophenotyping of clinical lung transplant recipients before and after LTx
  - › 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 transplantion model
- Bronchiolitis Obliterans (BOS)
  - › 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
  - › Construct 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 BOS
  - › Investigation of the role of donor and host macrophage activation in BOS-genesis
  - › Investigation of the role of bacterial or viral triggers in BOS-genesis

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
  - › Development of improved cannulas and cannulation methods for the establishment of suitable methods for connecting extra-and intracorporeal artificial lungs
  - › Development and testing of extracorporeal prototypes for long-term use in animal models
- Clinical program (lung failure of various origins)
  - › Development of new cannulation techniques
  - › Evaluation of the use of "awake" ECMO in various diseases
- Extracorporeal life support in patients with pulmonary hypertension and right heart failure
  - › Extraction of tissue samples (pulmonary vessels)
  - › Basic research on pulmonary vascular remodeling

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
  - › Human iPS generation of transgenic reporter lines for monitoring the respiratory differentiation and genetic enhancement
  - › Execution of screens for the identification of drugs and RNAs which facilitate respiratory differentiation of iPS cells
  - › Optimization of endothelial differentiation and enrichment of generated iPS-ECs

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
  - › Successful validation of the system in terms of immunomodulation after transplantation

Goal 5 - Healthcare Management

- Analysis of the supply situation of patients with terminal lung disease (ELD) and patients after lung transplantation
  - › Data collection according to special requests
  - › Data evaluation / merge of data from clinical and ambulatory sectors as well as from BREATH and CPC-M

Major Accomplishments Updated Through 2014

Transplantation

» Improved donor-recipient matching (Sommer W et al. J Heart Lung Transplant 32:1065, 2013) and treatment strategies for primary graft dysfunction in lung transplantation (Sommer et al. Transplantation 97:1185, 2014).
» Development of a relevant experimental model for chronic lung allograft dysfunction (Atanasova et al, J Heart Lung Transplant 32: 1131, 2013).
» Characterization of chronic lung allograft dysfunction subtypes (Greer et al. Am J Transplant. 13:911, 2013; Verleden et al. Am J Transplant 2015 Apr 30. doi: 10.1111/ajt.13281)
» Introduction of lung allocation score based allocation in Germany (Gottlieb et al. Am J Transplant 14:1318, 2014)

ECMO

» Preliminary work on an ex vivo immune modulation approach, presenting the possibility of HLA silencing to prevent an allogeneic immune response. (Wiegmann et al. Biomaterials 35:8123, 2014).
» Identification of effective strategies to prevent biofilm formation for the biohybrid lung (Wiegmann et al. Biomaterials 35:8123, 2014).
» Exploration of microbial contamination of membrane oxygenators in a clinical setting and establishment of adequate therapy for high-risk patients (Orszag et al. J Clin Microbiol 52:307, 2014; Kühn et al. ASAOI J 59:368, 2013).
» Establishment of awake ECMO in non-intubated patients as a bridge to lung transplantation (Olsson et al. Am J Transplant 10:2173, 2010; Fuehner et al. Am J Respir Crit Care Med 185:763, 2012) and translation to other indications, such as ARDS (Hoeper et al. Intensive Care Med 39:2056, 2013; Wiesner et al. Eur Resp J 40:1296, 2012).
» New concept of perioperative management using ECMO rather than heart-lung machine support (Ius et al. J Thorac Cardiovasc Surg 144:1510, 2012).
» Visualization of the ECMO watershed in patients with cardiac failure (Hoeper et al. Circulation 2:864, 2014).
» Development of biocompatible gas exchange membranes, including coating techniques for enhancing endothelialization; identification of endothelial cell sources and development of endothelial cell seeding protocol for hollow fiber gas-exchange membranes. (Hess et al. Tissue Eng Part A 16:3043, 2010; Kauffeldt et al. ISDEIV 1-4, 2012; Möller et al. J Org Chem 9:270, 2013; Hess et al. J Biomed Mater Res A 102:1909, 2014; Wiegmann et al. Biomaterials, 35:8123, 2014).

Regeneration

» Efficient differentiation protocol for the generation of endothelial cell types from human pluripotent stem cells (hPSCs) under scalable culture conditions established to provide sufficient cells e.g. for seeding of membranes for extracorporeal oxygenation. (Kempf et al. Stem Cell Reports 3:1132, 2014; Schmeckebier et al, Tissue Eng Part A, 19:938, 2013; Beekman et al, J Cyst Fibros, 13:363, 2014).
» Efficient generation of reporter cell lines by designer nuclease-mediated homologous recombination established and used as tools for protocol optimization and high throughput screenings; generation of early lung progenitor and mature lung cells from hPSCs achieved (Merkert et al. Stem Cell Reports 2:107, 2014).

Ex vivo Lung Perfusion

» Miniaturization of the ex vivo lung perfusion system in a small animal model (rat) as a working system to establish ex vivo therapies for different indications (Ciubotaru & Haverich, Eur Surg Res 54:64, 2014).
» First-in-man portable ex vivo lung perfusion for lung preservation in clinical transplantation (Warnecke et al. Lancet 380:1851, 2012).

Imaging

» Set up and testing of 2 variants of Optical Coherence Tomography for imaging of alveolar dynamics of rodent lungs in vivo and in isolated lungs. (Keller et al. J Appl Phyisol 113:975, 2012).

Health Care & Economics

» Comprehensive evaluation of cost reimbursement for LTx in complex recipients and recommendations for improved grouping and adequate reimbursement. (Vogl M et al. Eur Resp J 44,Suppl 58:1430, 2014)

Highlighted Publications, Lead by DZL Faculty - updated through 2014

Gottlieb J, Greer M, Sommerwerck U, Deuse T, Witt C, Schramm R, Hagl C, Strueber M, Smits JM. Introduction of the lung allocation score in Germany. Am J Transplant 14:1318, 2014 (BREATH, CPC-M)

Herold S, Hoegner K, Vadász I, Gessler T, Wilhelm J, Mayer K, Morty RE, Walmrath HD, Seeger W, Lohmeyer J. Inhaled granulocyte/macrophage colony-stimulating factor as treatment of pneumonia-associated acute respiratory distress syndrome. Am J Respir Crit Care Med 189:609, 2014 (UGMLC)

Hoeper MM, Tudorache I, Kühn C, Marsch G, Hartung D, Wiesner O, Boenisch O, Haverich A, Hinrichs J. Extracorporeal membrane oxygenation watershed. Circulation 130:864, 2014 (BREATH)

Wiegmann B, Figueiredo C, Gras C, Pflaum M, Schmeckebier S, Korossis S, Haverich A, Blasczyk R. Prevention of rejection of allogeneic endothelial cells in a biohybrid lung by silencing HLA-class I expression. Biomaterials 35:8123, 2014 (BREATH)

Atanasova S, Hirschburger M, Jonigk D, Obert M, Petri K, Evers A, Hecker A, Schmitz J, Kaufmann A, Wilhelm J, Chakraborty T, Warnecke G, Gottlieb J, Padberg W, Grau V. A relevant experimental model for human bronchiolitis obliterans syndrome. J Heart Lung Transplant 32:1131, 2013 (BREATH, UGMLC)

Greer M, Dierich M, De Wall C, Suhling H, Rademacher J, Welte T, Haverich A, Warnecke G, Ivanyi P, Buchholz S, Gottlieb J, Fuehner T: Phenotyping established chronic lung allograft dysfunction predicts extracorporeal photopheresis response in lung transplant patients. Am J Transplant 13:911, 2013 (BREATH)

Lachmann N, Happle C, Ackermann M, Lüttge D, Wetzke M, Merkert S, Hetzel M, Kensah G, Jara-Avaca M, Mucci A, Skuljec J, Dittrich AM, Pfaff N, Brennig S, Schambach A, Steinemann D, Göhring G, Cantz T, Martin U, Schwerk N, Hansen G*, Moritz T*. Gene Correction of Human Induced Pluripotent Stem Cells Repairs the Cellular Phenotype in Pulmonary Alveolar Proteinosis. Am J Respir Crit Care Med 189:176, 2013 (BREATH) *denotes shared senior authorship

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. Am J Respir Crit Care Med 185:763, 2012 (BREATH)

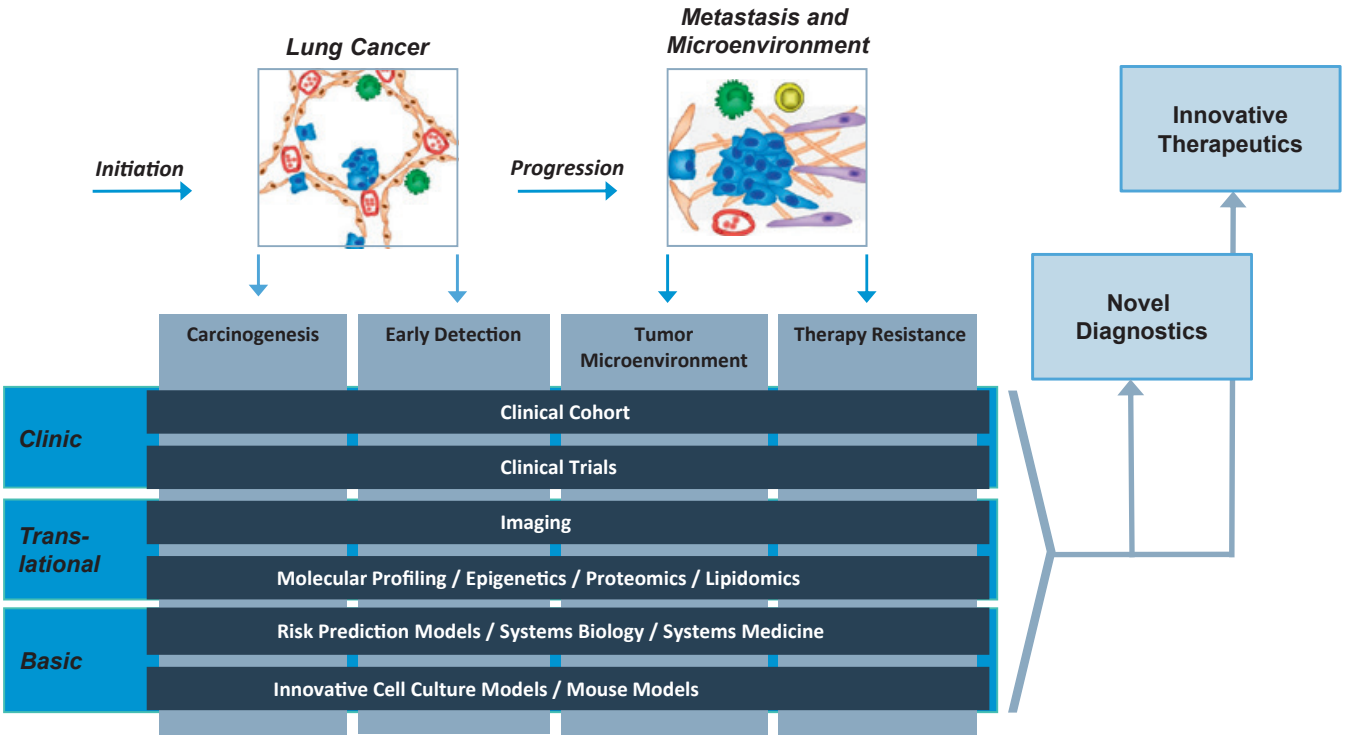
Warnecke G, Moradiellos J, Tudorache I, Kuhn C, Avsar M, Wiegmann B, Sommer W, Ius F, Kunze C, Gottlieb J, Varela A, Haverich A: Normothermic perfusion of donor lungs for preservation and assessment with the Organ Care System Lung before bilateral transplantation: a pilot study of 12 patients. Lancet 380:1851, 2012 (BREATH)

Number of papers published by DZL Faculty in 2014 - Disease Area ELD: 33

Lung Cancer

Disease Area Leaders	Prof. Ursula Klingmüller (TLRC)
	Prof. Michael Thomas (TLRC)
Participating DZL Partner Sites	ARCN, BREATH, CPC-M, TLRC
Number of Participating DZL Faculty	34

Lung cancer is a high incidence and high mortality disease. The two main lung cancer types are small-cell-lung carcinoma (SCLC; 20-30% of cases) and non-small cell lung carcinoma (NSCLC; 70-80% of cases). Patients presenting with SCLC have a particularly poor prognosis, and almost 40 % of NSCLC-patients present with metastases at time of diagnosis. Surgery, radiation, chemotherapy, and on a limited scale, targeted treatments — alone or in combination — are used to treat lung cancer. Limited knowledge of which individual molecular markers impact the propagation and spread of the disease impedes the development and use of targeted therapies; hence the treatment success is very variable. Our research focuses on the identification of relevant molecular markers urgently needed to advance matching of targeted treatments to patients, with the ultimate goal of developing personalized therapies to improve patient outcomes. Lung cancer research at the DZL is an interdisciplinary and integrative program exploring clinically well characterized sample sets with epidemiologic, genetic, epigenetic and systems biology approaches.



Goals Followed in 2014 – Lung Cancer

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

- Changes in methylation patterns
  - › Analysis of epigenetic changes and consequences for cell growth
- Epigenetic Lung Cancer Markers
  - › Identification of candidate gene list
  - › Establishment of a lung cancer risk prediction model
- 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)
  - › Identification of hormone receptor binding sites using ChIP-Seq technology
- Comparative analysis of DNA methylation profiles
  - › Identification of differential methylation profiles in the transition of COPD to lung cancer
  - › Investigation of epigenetic predisposition for 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
  - › Establish an integrative mathematical model for signal transduction, gene expression and cell migration
  - › 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 of prognosis determining molecular patterns
  - › Prediction and confirmation of mechanisms driving early metastasis
  - › Building a patient cohort
- Clinical Validation of Biomarkers for Early Metastasis
  - › Validation of predictive biomarkers in clinical studies
  - › Development of predictive prognosis and outcome parameters

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
  - › Predicting the effects of treatment combinations in vitro
- Characterization of the response to systemic and radiation therapy
  - › Analysis of tumor response by morphological and functional imaging
  - › Elucidating the mechanisms of therapy resistance
  - › 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
  - › Validation of the models predicting development of and overcoming therapy resistance
  - › Defining biomarkers to guide therapy
- 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

Major Accomplishments Updated Through 2014

Deregulation of TGF-β signaling in lung cancer, mechanisms of tumor suppression and tumor heterogeneity

» Comprehensive molecular profiling of lung adenocarcinoma (Cancer Genome Atlas Research Network, Nature 511:543, 2014); phosphodiesterase-4 promotes proliferation and angiogenesis of lung cancer by crosstalk with HIF (Pullamsetti et al., Oncogene 32:1121, 2013); dissection of p53 DNA binding mutants (Schlereth et al., PLoS Genet 9:e1003726, 2013; Timofeev et al., Cell Reports 3:1512, 2013); monitoring clonal tumor evolution during metastasis (Charles et al., Nat Commun 5:3981, 2014); long noncoding RNA TARID directs demethylation of TCF21 (Arab et al., Mol Cell 55:604, 2014)

Establishment of patient cohorts across DZL sites

» Harmonization of cohort assembly: Development of a common lung cancer data format and validation of biomaterial procurement strategies (Marwitz et al., Lab Invest 94:92, 2014; Shevchuk et al, J Proteome Res 13:5230, 20144)

Progress in predictive diagnostics - biomarkers

» Adenocarcinoma growth patterns are associated with prognosis and molecular alterations (Warth et al. J Clin Oncol 30:1438, 2012; Warth et al. Eur Resp J 43:872, 2014); serum miRNA-142-3p is associated with early relapse in adenocarcinoma (Kaduthanam et al., Lung Cancer 80:223, 2014); epigenetic screen identifies genotype-specific promoter DNA methylation and oncogenic potential of CHRNB4 (Scherf et al., Oncogene 32:3329, 2013); prognostic impact of IGF-1 pathway alterations in lung cancer (Reinmuth et al., Human Pathol 45:1162, 2014)

Patient outreach and participation in phase III trials

» Progression on platinum-based therapy in NSCLC - REVEL (Garon et al., Lancet 384:665, 2014), Ceritinib in ALK-rearranged NSCLC - Ascend (Shaw et al., N Engl J Med 370:1189, 2014), Docetaxel plus nintedanib in NSCLC - LUME-Lung 1 (Reck et al., Lancet Oncol 15:143, 2014)

Highlighted Publications, Lead by DZL Faculty - updated through 2014

Lindroth AM, Schäfer A, Oakes C, Weichenhan D, Lukanova A, Lundin E, Risch A, Meister M, Dienemann H, Dyckhoff G, Herold-Mende C, Grummt I, Niehrs C, Plass C. Long noncoding RNA TARID directs demethylation and activation of the tumor suppressor TCF21 via GADD45A. Mol Cell. 55:604, 2014 (TLRC)

Charles JP, Fuchs J, Hefter M, Vischedyk JB, Kleint M, Vogiatzi F, Schäfer JA, Nist A, Timofeev O, Wanzel M, Stiewe T. Monitoring the dynamics of clonal tumour evolution in vivo using secreted luciferases. Nat Commun 5:3981, 2014 (UGMLC)

Reck M, Kaiser R, Mellemgaard A, Douillard JY, Orlov S, Krzakowski M, von Pawel J, Gottfried M, Bondarenko I, Liao M, Gann CN, Barrueco J, Gaschler-Markefski B, Novello S; for the LUME-Lung 1 Study Group. Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small-cell lung cancer (LUME-Lung 1): a phase 3, double-blind, randomized controlled trial. Lancet Oncol 15:143, 2014 (ARCN)

Edelman MJ, Schneider CP, Tsai CM, Kim HT, Quoix E, Luft AV, Kaleta R, Mukhopadhyay P, Trifan OC, Whitaker L, Reck M. Randomized phase II study of ixabepilone or paclitaxel plus carboplatin in patients with non-small-cell lung cancer prospectively stratified by beta-3 tubulin status. J Clin Oncol 31:1990, 2013 (ARCN)

Kreuter M, Vansteenkiste J, Fischer JR, Eberhardt W, Zabeck H, Kollmeier J, Serke M, Frickhofen N, Reck M, Engel-Riedel W, Neumann S, Thomeer M, Schumann C, De Leyn P, Graeter T, Stamatis G, Zuna I, Griesinger F, Thomas M, TREAT Investigators. Randomized phase 2 trial on refinement of early-stage NSCLC adjuvant chemotherapy with cisplatin and pemetrexed versus cisplatin and vinorelbine: the TREAT study. Ann Oncol 24:986, 2013 (ARCN, TLRC)

Huber RM, Reck M, Thomas M: Current status of and future strategies for multimodality treatment of unresectable stage III nonsmall cell lung cancer. Eur Respir J, 42:1119, 2013 (ARCN, CPC-M, TLRC)

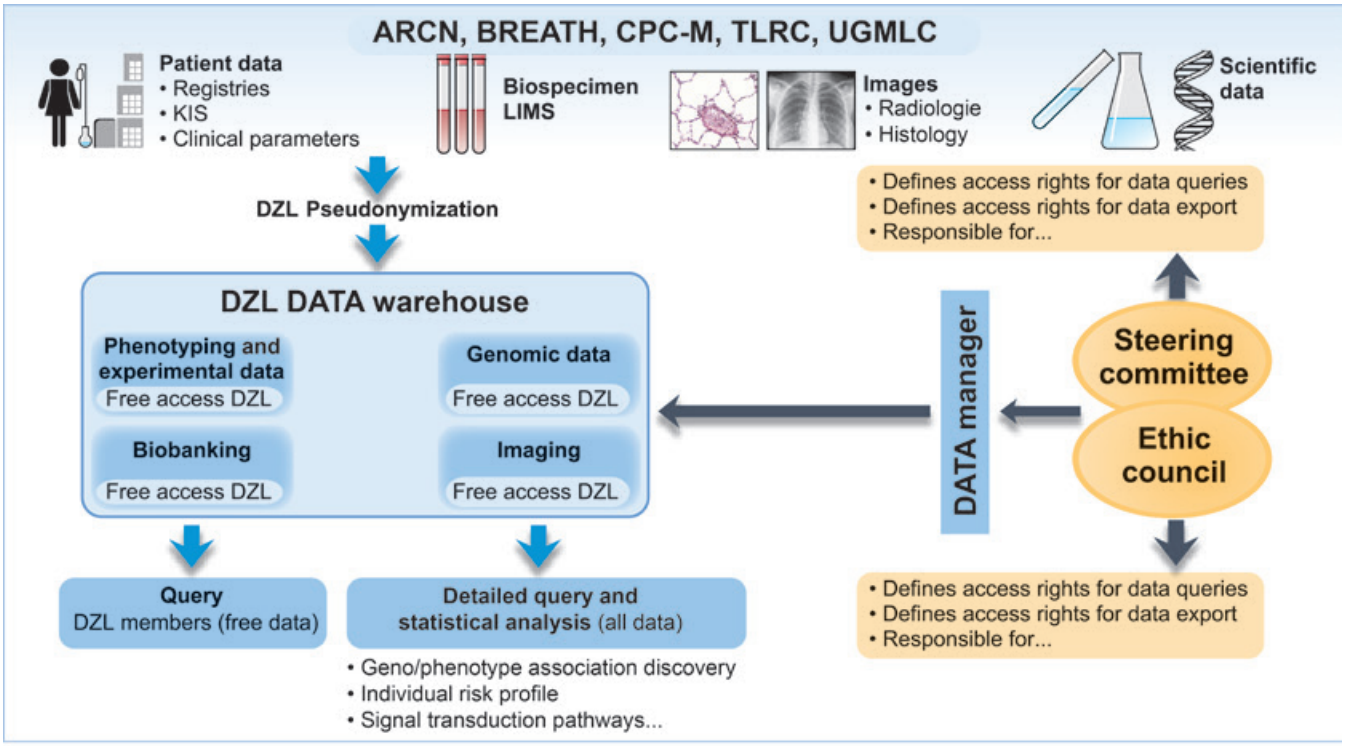
Reck M, Heigener DF, Mok T, Soria JC, Rabe KF. Management of non-small-cell lung cancer: recent developments. Lancet 382:709, 2013 (ARCN)

Number of papers published by DZL Faculty in 2014 - Disease Area LC: 109

Platform Biobanking

Scientific Coordinators	Prof. Dr. Andreas Günther (UGMLC)
	Dr. Thomas Muley (TLRC)
Participating DZL Partner Sites	ARCN, BREATH, CPC-M, TLRC, UGMLC
Number of Participating DZL Faculty	13

The DZL Disease Areas are supported by an extensive network of central infrastructure including the Platform Biobanking. The overall aim of the DZL Platform Biobanking is the collection and storage of biospecimen and associated data of different pulmonary diseases, with the intention of facilitating access for research purposes within and outside the DZL. Ethical and data protection rules apply. All DZL sites contribute to the Platform Biobanking and the focus is on the harmonization of procedures, quality control and data management.



Accomplishments Updated Through 2014

Implementation of a DZL biobanking portal
www.dzl.de/index.php/en/research/platforms/biobanking

Implementation of a database

» Implementation of a database of existing (retrospective) biomaterials, covering type and storage location, contact address, consent level, existing ethics vote, and phenotyping data, linked to the biobanking portal and connected to TMF e. V. and BBMRI catalogues

Development of the following documents and procedures for the prospective biomaterial collection:

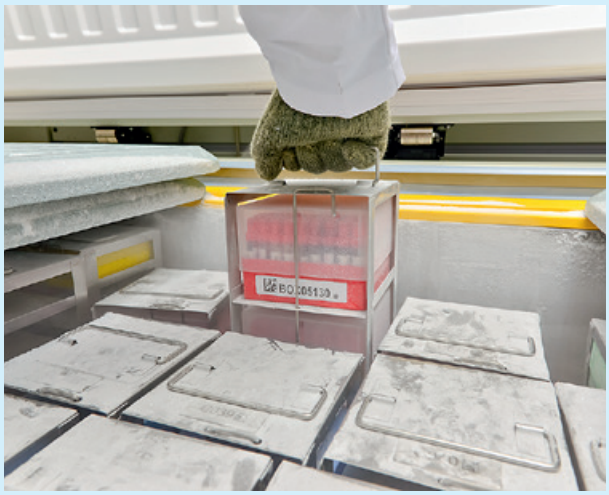
» DZL Platform Biobanking by-laws and Material Request Form, approved by DZL directors
» DZL-wide, harmonized broad consent form, based on most recent standards, first positive ethical votes granted by the respective ethics committees
» DZL data protection concept, based on most recent standards, as adopted by the TMF
» Harmonized SOPs for development of these documents and for single procedures related to biobanking
» Software solutions for DZL centralized Pat- and Lab-ID generation
» DZL data management structure including the DZL data warehouse

Representation of DZL platform and data management/dissemination of achievements

» National meetings (e.g., Deutsches Biobankensymposium, DZL annual meeting and International Symposium, Deutsche Gesellschaft f. Pathologie, Deutsche Gesellschaft für Medizinische Informatik, Biometrie und Epidemiologie)Publications (e.g., homepage Lung Information Service; publications referring to the biobank)
» Working group Biobanking of TMF e. V. and German Biobank Node (GBN)

Coordination of the biobanking and data warehouse concepts with the other DZGs

» Agreement to hold regular meetings (twice/year) to coordinate biobank activities and to harmonize Biobanking, IT and data management across the DZGs
» Agreement to implement a DZG Biobank catalogue
» Agreement to use laboratory information and management systems (LIMS) for the quality assured management of biospecimens
» Implementation of working groups "sample catalogue" and "LIMS"
» Agreement to implement individual state-of-the-art data protection concepts based on the TMF template
» Agreement to improve the interoperability of existing data management systems at different DZGs in view of implementing a DZG-wide data warehouse
» Agreement to improve quality management aspects, including implementation of a DZG Master SOP collection
» Agreement to initiate joint public relations activities (flyers, movies, joint publications)



Top 10 Publications with contribution of the Platform Biobanking

Marwitz S, Kolarova J, Reck M, Reinmuth N, Kugler C, Schädlich I, Haake A, Zabel P, Vollmer E, Siebert R, Goldmann T, Ammerpohl O. The tissue is the issue: improved methylome analysis from paraffin-embedded tissues by application of the HOPE technique. Lab Invest 94: 927, 2014 (ARCN)

Meister M, Belousov A, Xu EC, Schnabel P, Warth A, Hoffmann H Dienemann H, Riedlinger J, Bodenmueller H, Zolg W, Herth FJF, Muley T. Intra-tumor Heterogeneity of Gene Expression Profiles in Early Stage Non-Small Cell Lung Cancer. J Bioinformatics Res Studies 1:1, 2014 (TLRC)

Warth A, Muley T, Dienemann H, Goeppert B, Stenzinger A, Schnabel PA, Schirmacher P, Penzel R, Weichert W. ROS1 Expression and Translocations in Non-Small Cell Lung Cancer: Clinicopathological Analysis of 1478 Cases. Histopathology 65:187, 2014 (TLRC)

Aumiller V, Balsara N, Wilhelm J, Guenther A, Königshoff M. WNT/β-catenin signaling induces interleukin 1β production by alveolar epithelial cells in pulmonary fibrosis. Am J Respir Cell Mol Biol 49:96, 2013 (CPC-M, UGMLC)

Korfei M, Henneke I, Markart P, von der Beck D, Ruppert C, Mahavadi P, Klepetko W, Fink L, Meiners S, Krämer O, Seeger W, Vancheri C, Guenther A. Comparative Proteome Analysis of Lung Tissue from Patients with Idiopathic Pulmonary Fibrosis (IPF), Non-specific Interstitial Pneumonia (NSIP) and Organ Donors. J Proteomics 85:109, 2013. (CPC-M, UGMLC)

Nkyimbeng T, Ruppert C, Shiomi T, Dahal B, Lang G, Seeger W, Okada Y, D'Armiento J, Günther A. Pivotal role of Matrix Metalloproteinase 13 in extracellular matrix turnover in Idiopathic Pulmonary Fibrosis. PLoS One 8:e73279; 2013 (UGMLC)

Pandey RC, Michel S, Schieck M, Binia A, Liang L, Klopp N, Franke A, von Berg A, Bufe A, Rietschel E, Heinzmann A, Laub O, Simma B, Frischer T, Genuneit J, Illig T, Kabesch M: Polymorphisms in extracellular signal-regulated kinase family influence genetic susceptibility to asthma. J Allergy Clin Immunol 131:1245, 2013 (BREATH)

Pedersen F, Marwitz S, Seehase S, Kirsten AM, Zabel P, Vollmer E, Rabe KF, Magnussen H, Watz H, Goldmann T. HOPE-preservation of paraffin-embedded sputum samples--a new way of bioprofiling in COPD. Respir Med 107:587, 2013 (ARCN)

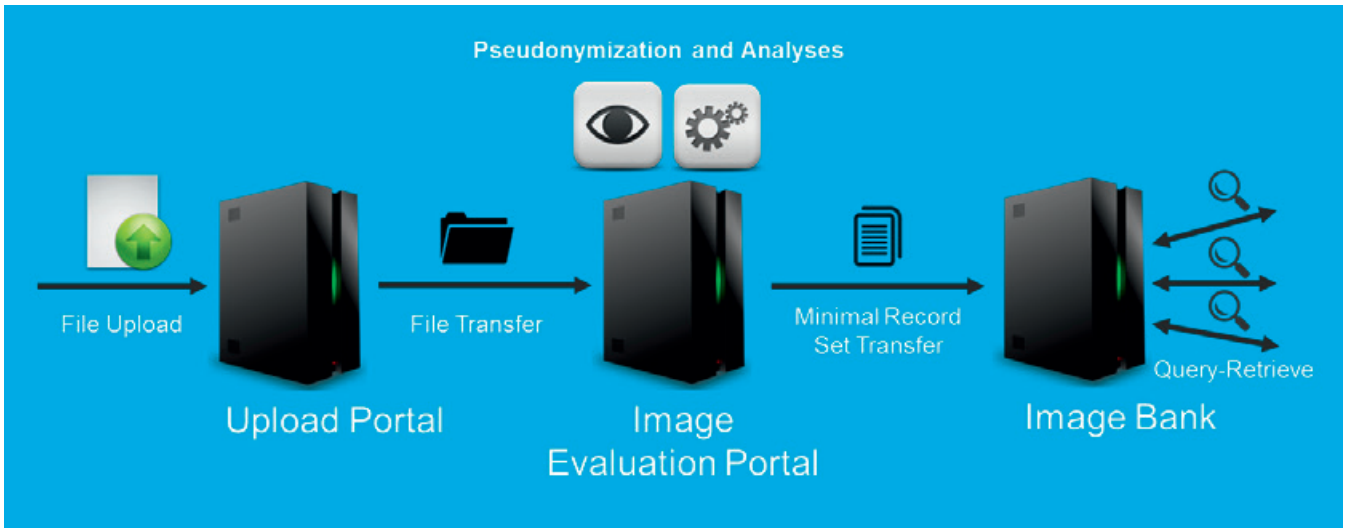
Schieck M, Michel S, Suttner K, Illig T, Zeilinger S, Franke A, Vogelberg C, von Berg A, Bufe A, Heinzmann A, Laub O, Rietschel E, Simma B, Frischer T, Genuneit J, Kerzel S, Kabesch M. Genetic variation in T(H)17 pathway genes, childhood asthma, and total serum IgE levels. J Allergy Clin Immunol 133:888, 2013 (BREATH)

Zeilinger S, Kühnel B, Klopp N, Baurecht H, Kleinschmidt A, Gieger C, Weidinger S, Lattka E, Adamski J, Peters A, Strauch K, Waldenberger M, Illig T. Tobacco smoking leads to extensive genome-wide changes in DNA methylation. PLoS One 8:e63812, 2013 (BREATH)

Platform Imaging

Scientific Coordinators	Prof. Dr. Hans-Ulrich Kauczor, TLRC
	Prof. Dr. Matthias Ochs, BREATH
	Prof. Dr. Heinz Fehrenbach, ARCN
Participating DZL-sites	ARCN, BREATH, CPC-M, TLRC, UGMLC
Number of participating DZL faculty	23

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.



Accomplishments Updated Through 2014

Set-up and Organization of the Imaging Platform

» Administration and Coordination
  › Establishment of the central coordination office at TLRC
» Communication strategy established
  › DZL Intranet, email distribution list, teleconferences
  › Meetings two times per year including a workshop

Image Bank

» Finalization of the Image Bank Bylaws (available via the DZL Intranet)
» Installation of the data warehouse solution i2b2 (Informatics for Integrating Biology & the Bedside) in compliance with the central DZL data warehouse (see Platform Biobanking)
» Implementation of
  › An Image File Management Portal
  › A function for automatic quantitative analysis (post-processing)
  › Functions to handle longitudinal studies
» Development of a minimum record set to index image files in the data warehouse and a SOP for pseudonymisation
» Implementation of a concept for the quantitative analysis of image data (post-processing)

Accomplishments in Technological Development

» Design-based stereology – Quality standards: animal model application
  › Basic concepts of design-based stereology
  › Pathology-based recommendations of quantitative parameters for various lung diseases
  › Worked examples with detailed calculations based on real raw data
  › Exemplified use of design-based stereology vs. classical cell profile counting in the analysis of endobronchial biopsies
  › Transfer of design-based stereology to animal models of broncho-pulmonary dysplasia from ARCN, BREATH to UGMLC

Fourier decomposition-MRI vs. 4D dynamic contrast-enhanced MRI and application in the disease areas CF, COPD, and PH

Early diagnosis of emphysema using in-vivo phase contrast imaging

Confocal 4D (z-stacks over time) live cell imaging of ex-vivo mouse lung tissue

FRET reporters for enzyme activity

» Protease activity in mouse models and CF and COPD patients

Implementation of morpho-functional MRI for non-invasive studies of early CF lung disease

Correlation of radio- and histo-morphological pattern of pulmonary adenocarcinoma

Set up of optical coherence microscopy (OCM) for imaging dynamic cellular processes in the airways as trans-tracheal OCM imaging in living mice; to be transferred to endoscopy

Use of Imaging in the Disease Areas - Examples

DA COPD

» COSYCONET sub-trial with CT and MRI (all DZL-sites involved)

» Pulmonary imaging for endoscopic treatment (ARCN, TLRC)

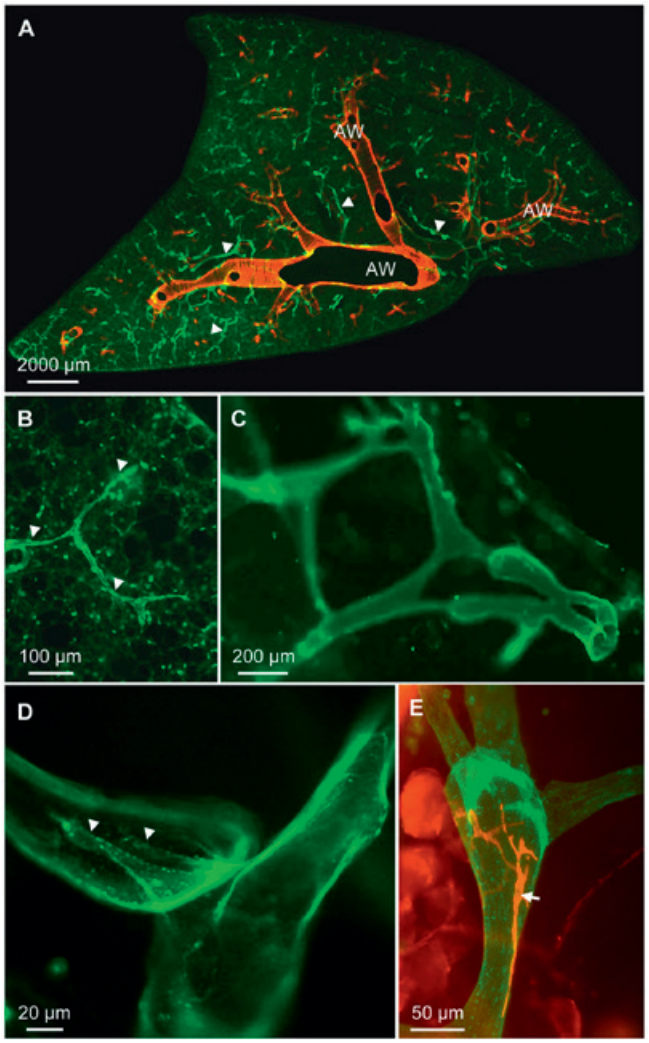
DA CF

» Observational study in infants with CF diagnosed by newborn screening (TRACK-CF cohort)

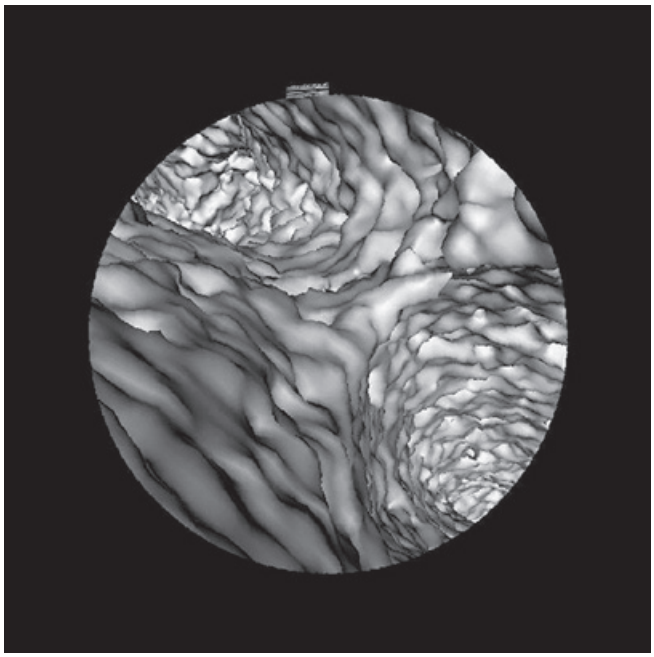
» Preventive hypertonic saline inhalation study (PRESIS) – (all DZL sites involved)

DA DPLD

» Attention to Infants with Respiratory Risks (AIRR) Study (CPC-M, UGMLC)



Immunohistochemistry of CD90/Thy-1 in murine precision cut lung slices (Source: T. Kretschmer et al., PLoS ONE. 2013; 8(2): e55201)



Virtual bronchoscopy: tracheal bifurcation and the right and left main bronchi

Highlighted Publ. from Microscopy and Radiology, lead by DZL Faculty – updated through 2014

Microscopy

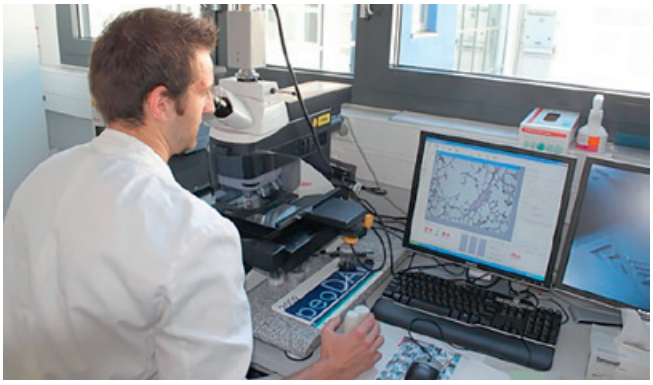
Bratu VA, Erpenbeck VJ, Fehrenbach A, Rausch T, Rittinghausen S, Krug N, Hohlfeld JM, Fehrenbach H, Cell counting in human endobronchial biopsies--disagreement of 2D versus 3D morphometry. PLoS One 9:e92510, 2014 (ARCN, BREATH)

Hu H-Y, Vats D, Vizovisek M, Kramer L, Germanier C, Wendt K U, Rudin M, Turk B,Plettenburg O, Schultz C. In vivo imaging of mouse tumors by a lipidated cathepsin S substrate. Angew Chem Int Ed 53:7669, 2014 (TLRC)

Madurga A, Mižíková I, Ruiz-Camp J, Vadász I, Herold S, Mayer K, Fehrenbach H, Seeger W, Morty RE, Systemic hydrogen sulfide administration partially restores normal alveolarization in an experimental animal model of bronchopulmonary dysplasia. Am J Physiol Lung Cell Mol Physiol 2014; 306:L684, 2014 (ARCN, UGMLC)

Muehlfeld C, Ochs M. Quantitative microscopy of the lung - a problem-based approach Part 2: Stereological parameters and study designs in various diseases of the respiratory tract. Am J Physiol Lung Cell Mol Physiol 305:L205, 2013 (BREATH)

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 nondestructive imaging using multiscale microcomputed tomography. Proc Natl Acad Sci U S A 109:17105, 2012 (BREATH)



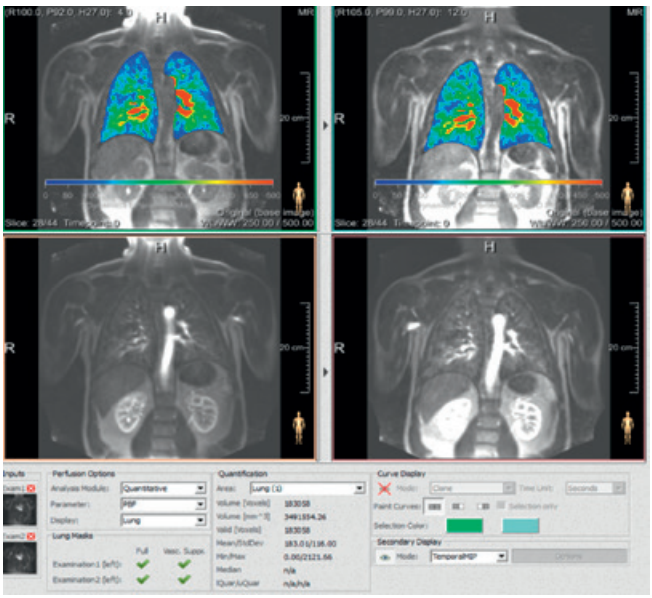
Laser Microdissection

Radiology

Lederlin M, Puderbach M, Muley T, Schnabel PA, Stenzinger A, Kauczor HU, Heussel CP, Herth FJ, Hoffmann H, Dienemann H, Weichert W, Warth A. Correlation of radio- and histomorphological pattern of pulmonary adenocarcinoma. Eur Respir J 41:943, 2014. (TLRC)

Wielpütz MO, Puderbach M, Kopp-Schneider A, Stahl M, Fritzsching E, Sommerburg O, Ley S, Sumkauskaite M, Biederer J, Kauczor HU, Eichinger M, Mall MA. Magnetic Resonance Imaging Detects Changes in Structure and Perfusion, and Response to Therapy in Early Cystic Fibrosis Lung Disease. Am J Respir Crit Care Med 189: 956, 2014 (TLRC)

Yaroshenko A, Meinel FG, Bech M, Tapfer A, Velroyen A, Schleede S, Auweter S, Bohla A, Yildirim AO, Nikolaou K, Bamberg F, Eickelberg O, Reiser MF, Pfeiffer F. Pulmonary Emphysema Diagnosis with a Preclinical Small-Animal X-ray Dark-Field Scatter-Contrast Scanner. Radiology 269: 427, 2013 (CPC-M)



Quantitative Analysis of Perfusions-MRI „Pulmo-MR“ (Source: MeVis/Bremen)

Clinical Trial Board and Clinical Trials

Scientific Coordinators	Prof. Dr. Norbert Krug (chair), BREATH
	PD Dr. Henrik Watz, ARCN
	Prof. Dr. Jürgen Behr, CPC-M
	Prof. Dr. Michael Thomas, TLRC
	Prof. Dr. H. Ardeschir Ghofrani, UGMLC

The DZL annually allocates a portion of its budget for innovative investigator initiated clinical trials. These flexible funds allow DZL investigators to respond to new advances in the field and translate those findings as quickly as possible to positive outcomes for patients. These funds are considered seed money, enabling the rapid transfer of novel findings into "first in human" investigations before external sponsoring is considered or may be achieved. Starting in 2012, annual internal calls for applications were distributed and the proposals were reviewed and evaluated by the DZL Clinical Trial Board in a competitive process. Final funding decisions are approved by the DZL Executive Board.

Ongoing DZL-funded clinical trials are found in the table below.

Coordinating PIs	Disease Area	DZL Partner Site(s) Involved	Title
Mall	CF	ARCN, BREATH, TLRC UGMLC	Randomized, double-blind, controlled pilot study on the safety of hypertonic saline as a preventative inhalation therapy in newborn patients with cystic fibrosis (PRESIS)
Thomas/Huber	LC	ARCN, CPC-M, TLRC	Comprehensive characterization of Non-Small Cell Lung Cancer (NSCLC) by integrated clinical and molecular analysis
Voswinckel/ Vogelmeier	COPD	ARCN, UGMLC	Clinical validation of the iNOS-EMAPII axis as biomarkers, predictors and novel targets in COPD
Vogelmeier	COPD	ARCN, BREATH, 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
Behr/Günther	DPLD	All	Exploratory efficacy and safety study of oral pirfenidone for progressive, non-IPF lung fibrosis (RELIEF in lung fibrosis)
Kauke/Winter/ Neurohr/ Schramm	ELD	BREATH, CPC-M	Impact of de-novo donor-specific antibodies on short- and long-term survival following single and double lung transplantation
Herold/ Lohmeyer/Welte	ALI	BREATH, UGMLC	Promotion of host defense and alveolar barrier regeneration by inhaled GM-CSF in patients with pneumonia-associated ARDS

DZL Investigators are involved in more than 250 clinical trials, addressing novel diagnostic and therapeutic approaches in lung diseases. Most of these studies are externally sponsored.

Technology Transfer Consortium

Chairs of the Consortium	Dr. Christian Stein, Managing Director of Ascenion
	Dr. Peter Stumpf, Managing Director of TransMIT
	Scientific Advisor
	Prof. Dr. Werner Seeger (Chairman and Speaker of the DZL)
Technology Transfer Agent	Dr. Annegret Zurawski (Manager of DZL site BREATH)

Efficient and effective exploitation of research results remains a key priority of the DZL. The DZL Technology Transfer Consortium, founded in 2013, is an important part of that strategy and provides key services to DZL members including:

- Collection of information regarding invention disclosures, patent applications, type and number of license agreements, and amount of technology transfer related revenue at DZL partner institutions
- Abstract screening services for DZL meetings
- Abstract screening "hotline" for DZL scientists on an as-needed basis
- Exploitation contract review
- Providing counsel regarding preparation for scientific advice meetings with BfArM with the aim of minimizing potential regulatory failures

All partners in the consortium are tech transfer organizations of DZL partners.

The institutions participating in the DZL TechnologyTransfer Consortium are:

ascenion

EMBLEM TECHNOLOGY TRANSFER

Max-Planck-Innovation

technology transfer heidelberg

dkfz. DEUTSCHES KREBSFORSCHUNGSZENTRUM IN DER HELMHOLTZ-GEMEINSCHAFT

Fraunhofer

TransMIT Gesellschaft für Technologietransfer mbH

The DZL Technology Transfer Consortium screened all submitted abstracts for the 2014 Annual Meeting and identified several that had potential intellectual property considerations. In addition, the DZL organized a panel discussion focusing on the interface between science and industry at the DZL International Symposium in Hannover "Regeneration and Beyond: BREATH meets REBIRTH" in May 2014, in which several members of the DZL Technology Transfer Consortium participated.

DZL Faculty, Members of the Technology Transfer Consortium and Industry Representatives participated in a panel discussion "What the industry wants from science and vice versa" at the DZL International Symposium in Hannover (May 2014).

Cooperation and Collaboration

3rd Annual DZL Internal Meeting

The 3rd Annual DZL Internal Meeting took place in Heidelberg at the historic Kongresshaus Stadthalle on January 21 and 22, 2014. With over 400 registered participants, DZL scientists and clinicians from all over Germany came together to discuss the latest findings in lung research from the DZL. Seven members of the DZL Scientific Advisory Board also participated in the meeting and were on hand to give feedback, advice, and help judge the 2nd Annual DZL Poster Contest. This year poster prizes were awarded to the best poster from the Platforms as well as to each Disease Area. Winners were selected from a field of close to 200 posters. The poster award winners were:

- Asthma and Allergy – Sabine Bartel, CPC-M
- COPD, Korbinian Ballweg, CPC-M
- Cystic Fibrosis, Ute Oltmanns, TLRC
- Pneumonia and Acute Lung Injury, Rory Morty, UGMLC
- Diffuse Parenchymal Lung Disease, Herbert Schiller, CPC-M
- Pulmonary Hypertension – prize shared by Prakash Chelladurai, UGMLC and Rebecca Schmidt, TLRC
- End-stage Lung Disease – Saskia Ulrich, BREATH
- Lung Cancer – Anja Schmall, UGMLC
- Platforms – Jens Hansen, TLRC

DZL International Symposium 2014

The 3rd International DZL Symposium took place in Hannover from May 8 – 10, 2014. Close to 350 lung researchers came from all over the world to discuss the latest approaches to research and therapy of lung diseases.

Co-organized by BREATH and the REBIRTH Cluster of Excellence (From Regenerative Biology to Reconstructive Therapy), the main focus of the symposium entitled 'Lung Regeneration and Beyond: BREATH meets REBIRTH' was on innovative techniques areas across different areas – transplantation, artificial organs, tissue engineering, regenerative therapies and stem cell research. In addition, there were sessions covering each Disease Area studied by the DZL.

The translation of scientific findings into clinical practice or industrial applications was a central theme of the symposium, attended by scientists, clinicians, politicians, industry representatives, and technology transfer officers. The collected abstracts of all oral and poster presentations at the symposium were published in a volume entitled '3rd International DZL Symposium: Lung Regeneration and Beyond – BREATH meets REBIRTH' (ISBN 978-3-00-045880-4) and the poster abstracts appeared in the June 2014 issue of the medical journal "Pneumologie".

Youth Development and Equal Opportunities

Training the next generation of lung researchers is a top priority, and the DZL takes a multi-faceted approach to support early career development.

DZL Mentoring Program

In 2014 the DZL mentoring program "Careers in Respiratory Medicine" was prepared and it was officially kicked off in early 2015. The mentoring program is focused on supporting highly motivated junior DZL scientists working in biomedical science and medicine. The program supports the fellows in their career advancement and aims to identify and develop future DZL and lung community leaders who are trained in scientific, management, and leadership skills. 11 mentor/mentee pairs were matched in 2014 with additional DZL faculty available to mentor as the program expands in the future years.

German-French Lung School

The German-French Lung School was launched in September 2013 and is managed by the CPC-M site. Through the creation of this program, students and postdocs engaged in lung research in France and Germany have the opportunity to learn new techniques, be exposed to different ways of scientific thinking and build a network of international contacts. Regular Winter and Summer Schools at both sites support the scientific exchange.

Equal Opportunities

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 is place on the active recruitment of female scientists to the DZL at every level – from the trainee to the advisory board member. Particular focus has been placed on increasing the number of female PIs in the DZL. The percentage of female PIs in the DZL has increased to 20% in 2014 up from only 14% in 2011 when the DZL was founded.

Graduate Training Programs

Graduate training programs emphasizing lung research are available at all DZL Sites.

DZL Site Kiel, Lübeck, Grosshansdorf & Borstel (ARCN)
- Graduate Centers at Universities of Kiel and Lübeck
- Graduate programs from DFG Excellence Initiative
- Borstel Biomedical Research School, fully devoted to lung research

DZL Site Hannover (BREATH)
- Hannover Biomedical Research School (HBRS)
- HBRS Structured Medical Doctors' Program (StrucMed Program)
- BREATH quarterly DZL colloquia

DZL site Munich (CPC-M)
- CPC Research School "Lung Biology and Disease"
- Munich Medical Research School
- Helmholtz Graduate School Environmental Health

DZL Site Heidelberg (TLRC)
- Hartmut Hoffmann-Berling International Graduate School of Molecular and Cellular Biology
- Research project opportunities in TLRC labs
- Monthly TLRC research seminar series

DZL Site Gießen, Marburg & Bad Nauheim (UGMLC)
- UGMLC School
- Molecular Biology and Medicine of the Lung (MBML Program, JLU Giessen)
- International Max Planck Research School for Heart and Lung Research (IMPRS-HLR, Max Planck Bad Nauheim)

DZL and the Public

The DZL has a highly active public relations strategy for both the scientific and general public including patient information events, scientific symposia, publications, a strong internet presence (www.dzl.de), and participation in national and international congresses. The homepage category "New this week in PubMed" presents a weekly update of novel publications from DZL scientists. A short film portrait about the DZL is available on the DZL homepage and via YouTube, too.

Highlights in 2014 included:

- Leading role in European Respiratory Society (ERS) International Congress in Munich: congress co-chair Prof. Dr. Oliver Eickelberg and co-chair Prof. Dr. Jürgen Behr, numerous prize winners, speakers, session chairs, and a DZL information booth in the "World Village"
- Strong showing at the 2014 German Respiratory Society (DGP) Congress in Bremen including an information booth, DZL speakers, session chairs, and prize winners
- 3rd DZL International Symposium in Hannover with ~ 350 lung researchers from all over the world
- Co-sponsoring of a session in Translational Medicine at 2014 World Health Summit in Berlin (with other DZGs)
- DZL Annual Report 2014 (in English and in German)
- DZL updates published in the blue pages ("DZL-Mitteilungen") of the Journal of the German Respiratory Society "Pneumologie"
- first quarterly DZL e-mail newsletter went out in spring of 2014
- Position statement published in "The Lancet Respiratory Medicine" on Benchmarks for Translational Research (Grether et al., Lancet Respir Med 2:e13, 2014)
- Contributions to "Weißbuch Lunge 2014" (Lung White Book, co-editorship DZL director T. Welte, Hannover)
- World's first monograph on mutant-specific therapies ("Mutation-specific therapies in cystic fibrosis – Current status and prospects") by DZL PI B. Tümmler has been published, written in collaboration with other DZL scientists like DZL director M. Mall
- Patient forums together with the Lung Information Service, including a two day event on Clean Air and Lung Health in cooperation with the European Lung Foundation (ELF, Healthy Lungs for Life Campaign) on the occasion of the ERS International Congress in Munich

Prizes and Awards

- **Prof. Dr. Oliver Eickelberg** (Director of CPC-M)
  Fellow of ERS* (FERS), elected in 2014
- **Prof. Dr. Roland Eils** (TLRC)
  Heidelberg Molecular Life Sciences Investigator Award
- **Prof Dr. H. Ardeschir Ghofrani** (UGMLC)
  Fellow of ERS (FERS), elected in 2014
- **Prof. Dr. Magdalena Götz** (CPC-M)
  Ernst Schering Prize 2014
- **Prof. Dr. Matthias Griese** (CPC-M)
  ERS Award for Rare Pulmonary Disease Research
- **Prof. Dr. Axel Haverich** (BREATH)
  Fritz Behrens Prize – for his life's work
- **Prof. Dr. Marius Hoeper** (BREATH)
  ERS Award for Lifetime Achievement in Pulmonary Hypertension
- **Prof. Dr. Sabina Janciauskiene** (BREATH)
  1st AstraZeneca Pneumology Award
- **Dr. Dr. Melanie Königshoff** (CPC-M)
  ERS Research Award on Idiopathic Pulmonary Fibrosis
- **Dr. Lars Lunding** (ARCN, Junior Sc.)
  Prize for the best PhD thesis in the field of pneumology by the "Deutsche Lungenstiftung e. V."
- **Sven Michel** (BREATH, Junior Sc.)
  2014 Research Prize of the German Respiratory Society (DGP) for outstanding work in clinical research (shared prize)
- **Dr. Vanessa Neuhaus** (BREATH, Junior Sc.)
  2014 Research Prize of the German Respiratory Society (DGP) for outstanding work in clinical research (shared prize)
- **Dr. Dorothea M. Peters** (UGMLC, Junior Sc.)
  2014 Research Prize of the German Respiratory Society (DGP) for outstanding work in basic science
- **Prof. Dr. Klaus F. Rabe** (Director of ARCN)
  Fellow of ERS (FERS), elected in 2014
- **Prof. Dr. Werner Seeger** (DZL Chairman, Director of UGMLC)
  - 2014 Dickinson W. Richards Memorial Medal of the American Heart Association
  - Von Behring-Röntgen-Research Medal – for his life's work
  - 2014 ERS Congress Chair Award – for his life's work
  - Fellow of ERS (FERS), elected in 2014
- **PD Dr. Jens Vogel-Claussen** (BREATH)
  Wilhelm-Conrad-Röntgen-Ring Prize
- **Prof. Dr. Claus Vogelmeier** (UGMLC)
  Fellow of ERS (FERS), elected in 2014
- **Dr. Arne Warth** (TLRC)
  2014 Else Kröner-Fresenius-Foundation Excellence Grant
- **Dr. Sina Webering** (ARCN, Junior Sc.)
  Young Investigator Award der ERS
- **Prof Dr. Tobias Welte** (Director of BREATH)
  Fellow of ERS (FERS), elected in 2014
- **Dr. Kristin Westphalen** (CPC-M)
  ERS Best Publication Maurizio Vignola Award for Innovation in Pneumology 2014 (shared prize)
- **Dr. Mark Oliver Wielpütz** (TLRC)
  Christiane Herzog Research Award

*Names sorted alphabetically; *ERS = European Respiratory Society*

f. l. t. r.: Professor Dr. T. Welte (DZL Director, DGP President in 2014) with the award winners Dr. D. Peters, Dr. V. Neuhaus and S. Michel (DZL Junior Scientists), who received the Research Prizes of the German Respiratory Society (DGP) in March 2014 in Bremen.

Professor Dr. W. Seeger (DZL Chairman) received the Von Behring-Röntgen-Research Medal for his life's work in October 2014 in Giessen (awarded by the former German Federal Minister and president of the Von Behring-Röntgen-Stiftung F. Bohl – on the left site).

Professor Dr. Axel Haverich (DZL DA Leader of the Disease Area "End Stage Lung Disease", on the left site) was honored with the renowned Fritz Behrens Prize for his life's work in June 2014 in Hannover.

Lung Information Service (LIS)

The Lung Information Service plays a key role in the DZL's General Public Outreach Strategy. Headquartered at the Helmholtz Zentrum München, the LIS maintains a website containing comprehensive, up-to-date, accurate and unbiased information on lung diseases accessible to the general public.

Special Topics Addressed by the Lung Information Service on their Website in 2014

- Advanced Lung Disease (January 2014)
- Hay Fever (February 2014)
- Bronchiectasis (March 2014)
- Fit for Everyday Life (April 2014)
- Lung Cancer (May 2014)
- Traveling with Oxygen (June 2014)
- Allergic Asthma (July 2014)
- Pneumothorax (August/September 2014)
- Patient Questions – Expert Answers (October 2014)
- Bronchodilators (November 2014)
- Surgical Procedures in Pulmonary Medicine (December 2014)

An important source of LIS information are articles published on patient-relevant topics in top journals, including an increasing proportion with DZL authorship. In addition, the LIS regularly publishes expert interviews on current issues in lung research, including in interviews with leading DZL scientists. The LIS also publishes on special topics, such as lung cancer, asthma, bronchiectasis, as well as diagnostic methods and therapies like transplantation and other lung surgeries. In addition to purely scientific content, it publishes information about patient-relevant events, literature recommendations to patients, and announcements of lung-relevant television and radio broadcasts.

From 2011-2014 the LIS published more than 400 news articles on its website www.lungeninformationsdienst.de. Furthermore the LIS offers a monthly newsletter and individual RSS feeds. In late 2011 a very popular series of patient information forums covering a breadth of topics from different lung diseases has started. In 2014 LIS and DZL sites held several patient forums, including a two day event on Clean Air and Lung Health in cooperation with the European Lung Foundation (ELF) on the occasion of the European Respiratory Society International Congress in Munich. The LID also actively interacts with patient organizations to receive feedback and suggestions for topics to cover.

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).

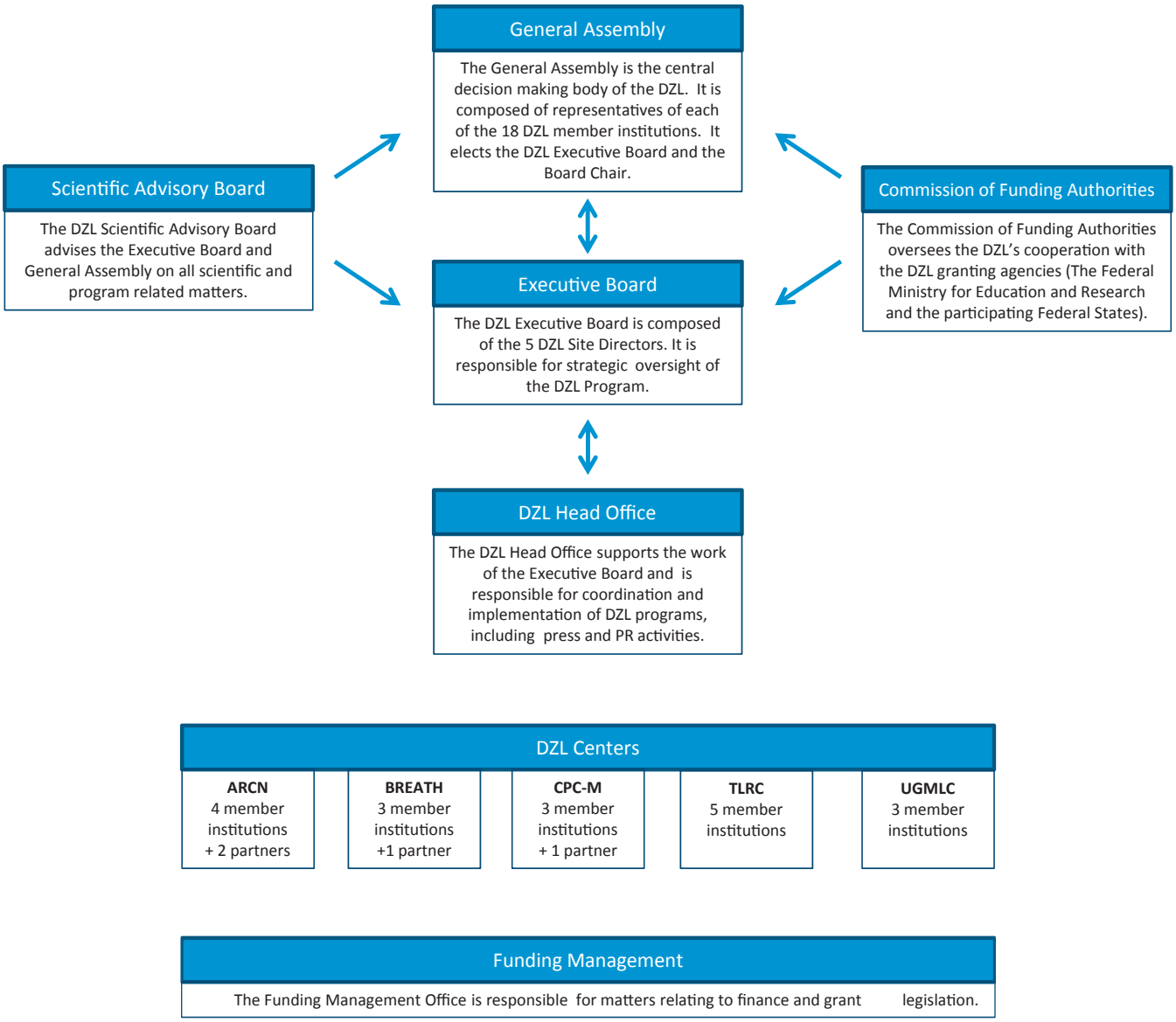
Over the long term, the strategic collaboration of leading scientists in the German Centers for Health Research will make Germany internationally more competitive as a science location and markedly more attractive for young researchers both within Germany and from around the world.

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 (DZL). 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

The six German Health Centers cooperate frequently in order to share their findings, exploit synergies, and promote the mission of the German government's framework health research program.

DZG DEUTSCHE ZENTREN DER GESUNDHEITSFORSCHUNG

DZL Organization



DZL Executive Board

- Prof. Dr. Werner Seeger (DZL Chairman and Speaker) – DZL Site Giessen, Marburg, Bad Nauheim (UGMLC)
- Prof. Dr. Oliver Eickelberg – DZL Site Munich (CPC-M)
- Prof. Dr. Marcus A. Mall – DZL Site Heidelberg (TLRC)
- Prof. Dr. Klaus F. Rabe – DZL Site Borstel, Großhansdorf, Kiel, Lübeck, (ARCN)
- Prof. Dr. Tobias Welte – DZL Site Hannover (BREATH)

DZL Head Office

- Megan Grether, PhD, Managing Director / Scientific Officer (till June 2015, since July 2015 provisionally: Dr. Sylvia Weissmann)
- Sabine Baumgarten, M. A., Project Coordinator and Public Relations

Scientific Advisory Board

Jacob I. Sznajder, MD (SAB Chair)
Chief, Division of Medicine-Pulmonary, Ernest S. Bazley Professor of Asthma and Related Disorders, Northwestern University Feinberg School of Medicine

Peter J. Barnes, MD
Head of Respiratory Medicine, Imperial College London

Rachel Chambers, PhD
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

Stuart Elborn, MD
Professor of Respiratory Medicine, Belfast City Hospital, Director Centre for Infection and Immunity and Dean, School of Medicine, Dentistry and Biomedical Sciences, 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
Former 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

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* resigned from his post for health reasons

Funding Management Office

Heads

- Dr. Dorothe Burggraf – Financial Department
- Dr. Stefan Echinger – Department of Operations & Support

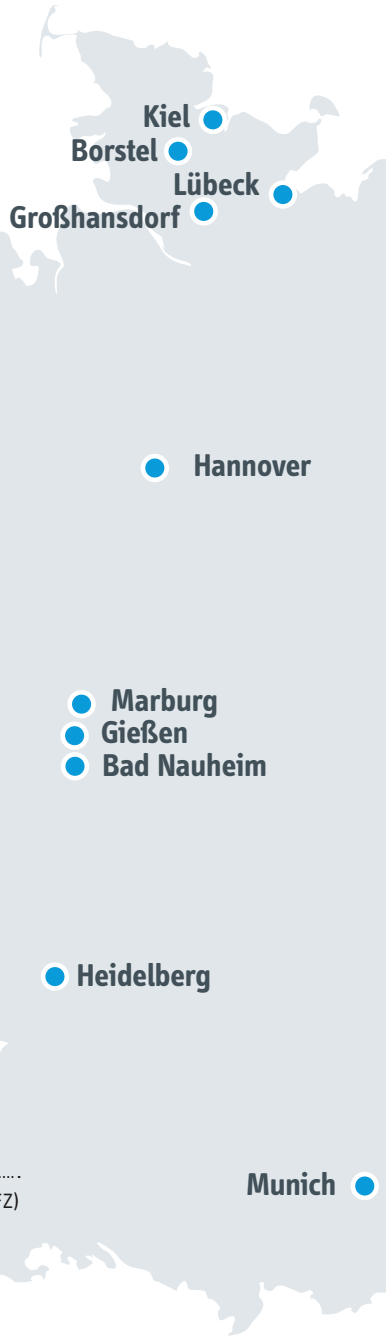
Commission of Funding Authorities

Participating Institutions

- Federal Ministry for Education and Research, BMBF, (Chair)
- Baden-Württemberg – Ministry for Science, Research, and Art
- Bavaria – Ministry for Education and Culture, Science and Art
- Hesse – Ministry for Science and Art
- Lower Saxony – Ministry for Science and Culture
- Schleswig-Holstein – Ministry for Social Affairs, Health, Science and Equality

DZL Cooperating Partners

The 18 DZL member institutions are shown on the following map.
Additionally the DZL has 4 associated partner institutions.



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

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

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

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

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

Associated partners are shown in grey

DZL Site 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
- Kiel University
- LungenClinic Grosshansdorf

Prof. Dr. Klaus F. Rabe

- Director of ARCN
- Medical Director of the LungenClinic Grosshansdorf
- Professor of Pneumology, Kiel University
- Chairman of the Institute for Lung Research (ILF)
- President of the European Respiratory Society (ERS) 2011/2012
- Fellow of ERS (FERS), elected in 2014
- Vice-President of the German Respiratory Society (DGP)

Contact

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Number of DZL Principal Investigators: 30

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 diseases. In keeping with the approach of the DZL, ARCN researchers pursue a holistic approach to study the lung, including disease pathogenesis, the progression 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)
- Leibniz 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 Respiratory Society, 2013–2015
- Fellow of ERS (FERS), elected in 2014

Contact

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Number of DZL Principal Investigators: 48

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), 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 Zentrum München – German Center for Environmental Health
- Ludwig Maximilian University Munich
- Munich University Hospital
- Asklepios Clinic Munich-Gauting

Prof. Dr. Oliver Eickelberg

- Director of CPC-M
- Chairman of the Comprehensive Pneumology Center
- Director of the Institute of Lung Biology and Disease, Helmholtz Zentrum München
- Professor of Experimental Pneumology at Ludwig-Maximilian University Munich
- Fellow of ERS (FERS), elected in 2014

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Number of DZL Principal Investigators: 42

Research Profile

At the Comprehensive Pneumology Center Munich (CPC-M), the Helmholtz Zentrum München, Ludwig Maximilian University Munich 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 disease world-wide. The Helmholtz Zentrum München is a renowned expert in bridging fundamental research and applied medical research with a strong focus on translational medicine in the area of lung disease. Ludwig Maximilian 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 (stem) cell biology, pharmacology, molecular pathology and clinical medicine in order to
develop new diagnostic tools and therapies. CPC-M scientists are coordinators for the Disease Areas "Diffuse parenchymal Lung Disease" and "Asthma and Allergy".

As an important link between clinical and experimental research the CPC-M operates the CPC outpatient unit where researchers and clinicians work close together to interlink scientific results and therapeutic approaches. In addition to its research program the CPC-M coordinates the German-French Lung School together with the CPC Research School and Graduate Program "Lung Biology and Disease". The CPC-M also operates the
Lung Information Service (www.lungeninformationsdienst.de) which is responsible for effective public and patient education and outreach about lung diseases.

Translational Lung Research Center Heidelberg (TLRC)

Heidelberg

- Heidelberg University Hospital
- Ruprecht-Karls-University, Heidelberg
- Thoraxklinik at Heidelberg University Hospital
- German Cancer Research Center (DKFZ)
- 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: 34

Research Profile

The Heidelberg Translational Lung Research Center (TLRC) is an interdisciplinary center for translational lung research in which physicians and scientists at the Heidelberg University Hospital and Medical Faculty of Heidelberg, the Thorax Clinic at the Heidelberg 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. Our common goal is to improve diagnosis and therapy of chronic lung diseases in children and adults by promoting the close collaboration and exchange of expertise between basic research and clinical science.

The research focus is on elucidating the mechanisms underlying common genetic and acquired chronic and malignant lung diseases such as cystic fibrosis, 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 cell- and animal models are used to investigate molecular causes of chronic airway diseases with a focus on the role of the airway epithelium. We make use of next generation-sequencing, as well as state-of-the-art immunology and molecular biology techniques. Results from these experiments will improve our understanding of airway mucus obstruction and chronic inflammation in cystic fibrosis and other chronic obstructive lung diseases, such as COPD and asthma. Systems biology is applied to improve our understanding of the molecular causes of lung cancer. Early clinical trials are conducted to make new diagnostic and therapeutic strategies 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 (DZL, 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)
- Fellow of ERS (FERS), elected in 2014

Contact

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Number of DZL Principal Investigators: 56

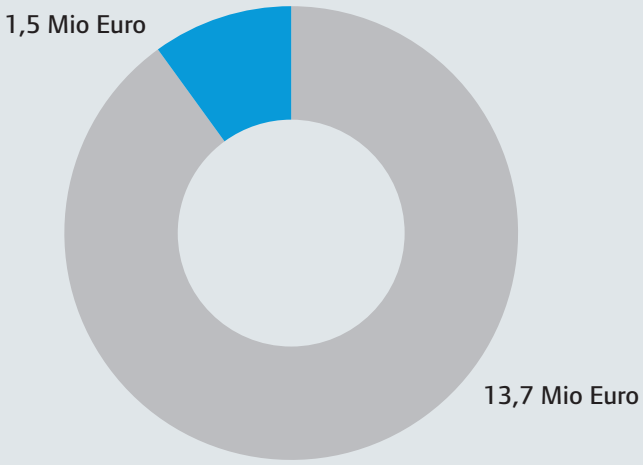
Research Profile, UGMLC

Translational research at the Universities of Giessen and Marburg Lung Center (UGMLC) deals with lung diseases caused by inflammatory and hyperproliferative processes. This includes research on the impact of environmental factors on the development of asthma as well as on the development and therapy of Chronic Obstructive Pulmonary Disease (COPD), with special focus on the alterations of airways and blood vessels. In the Disease Area Pneumonia and Acute Lung Injury (ALI), UGMLC concentrates on the role of innate immunity and inflammatory mechanisms in the acute disease and during resolution and regeneration. Molecular and cellular mechanisms that may help developing efficient regenerative therapies are studied in the Disease Areas Lung Fibrosis (DPLD) and Pulmonary Hypertension (PH).

The UGMLC partners complement one another by a close interplay of basic research and clinical research, which is based on the cooperation of the Max-Planck-Institute, the universities and the university hospital. Marburg focuses on the areas of asthma, COPD and lung cancer, Giessen on DPLD, COPD, CF and PH, where Giessen can be regarded as a national and international center. The Max-Planck-Institute 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. Further synergies result from cooperation with the other DZL sites as well as other networks (such as Asconet and Cosyconet) and local research consortia like the Cluster of Excellence Cardio-Pulmonary System (ECCPS).

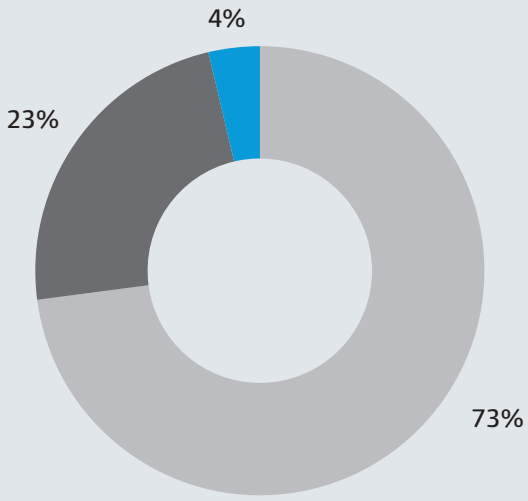
Within the DZL, UGMLC hosts the DZL Central Office and the DZL Biobank and Data Management Platform.

Financials and Personnel



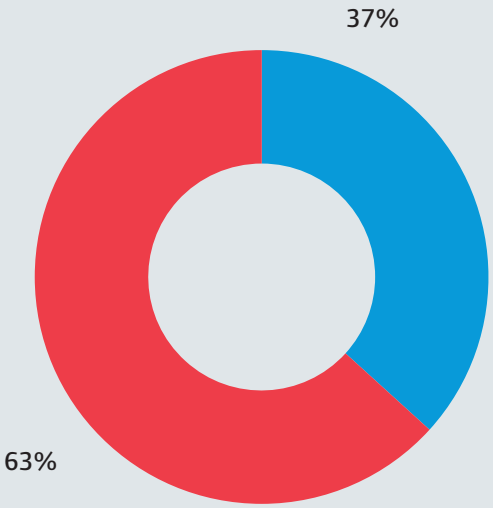
Total Funding

The total funding for the DZL in 2014 was 15.2 Million Euro. 90% was received from the Federal government and 10% from the five German states with participating DZL Centers. The Funding Management Office at the Helmholtz Center Munich distributed the project funding to the respective partner institutions. Across the eight disease areas studied by DZL scientists more than 50 major research projects are addressed.



Cost Breakdown – DZL 2014 Expenses

- Personnel
- Consumables
- Equipment



Cost Breakdown – DZL e. V. Expenses

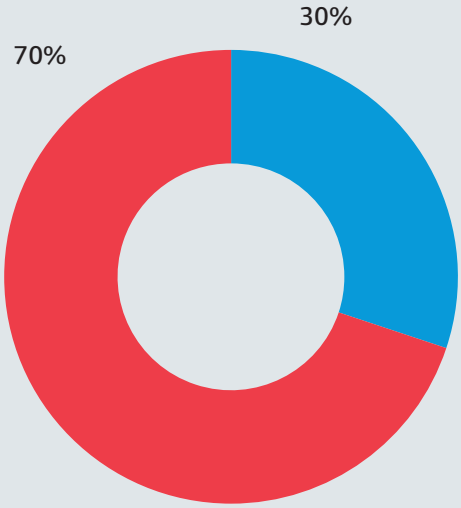
- Personnel
- Consumables

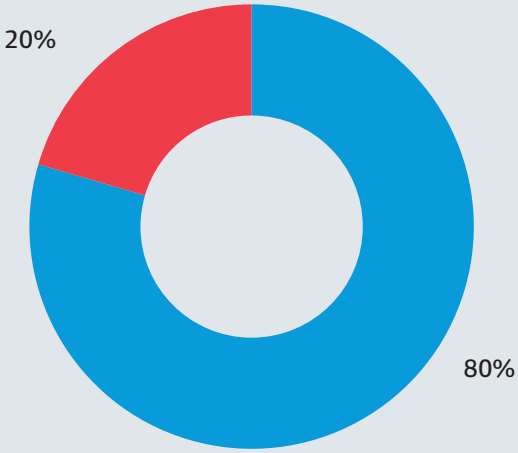
The DZL e. V. is financed through membership fees collected from each member institution, amounting to €325,000 in 2014. The 2014 Annual Financial Statement and Year-end Close of the DZL e. V. was conducted by the firm Haas & Haas.

Personnel – DZL 2014 Expenses

- male
- female

In 2014, 339 employees (210 Full Time Equivalents) were directly financed with DZL funds across the five partner centers, an increase of 88 people when compared to 2013. Of the 339 funded employees, 188 were scientists and 151 support staff.





Principal Investigators – DZL 2014 Expenses

- male
- female

There are 210 affiliated principal investigators (PIs) in the DZL, although not all of them receive DZL funds. In 2014, 43 women (20%) were DZL PIs. The DZL continues to actively promote and recruit women to its faculty.

Masthead

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(Sept. 2012 - June 2015: Megan Grether, PhD)

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Photos/Graphics: DZL/DZL partners, except: Cover: iStock/Eraxion, p. 3: iStock/Neustockimages , p. 41 left: T. Kretschmer/PLoS One, p. 42 right: MeVis/Bremen, p. 49 left: European Respiratory Society, p. 49 right: World Health Summit, p. 51: Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin e. V., p. 51 middle: Von Behring-Röntgen-Stiftung/Christian Stein, p. 52: Lungeninformationsdienst/Helmholtz Zentrum München

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