DZL
Deutsches Zentrum für
Lungenforschung

DZG DEUTSCHE ZENTREN
DER GESUNDHEITSFORSCHUNG

# German Center for Lung Research

ANNUAL REPORT

2015

# Translational Research to Combat Widespread Lung Diseases

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# 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 annual expenditure and, when factoring in loss of production and disability-adjusted life years (DALY), 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 as yet. 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 in the fight against some of the world's biggest killers. The recent international scientific expert evaluation of the first four years since its foundation attests that the DZL has made "enormous progress" and accomplished "substantial achievements". Furthermore, the board of reviewers states that "the DZL has established a worldwide leading powerhouse of investigators, tools, cohorts, and network of collaborations". In this report we summarize selected highlights of last year's activities within the DZL following its mission to fight respiratory diseases.

On behalf of the German Center for Lung Research,

# 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 in the aim of developing new and innovative therapies for patients with lung disease.

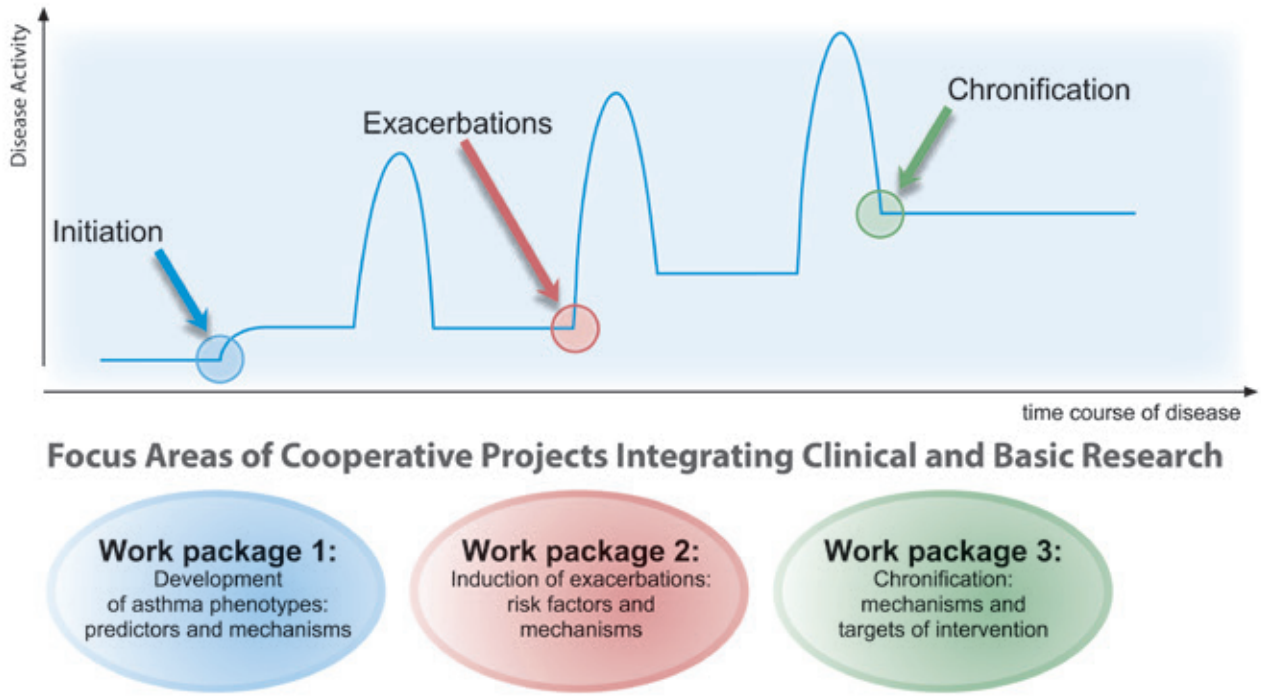
In 2015, the DZL included 218 principal investigators and their research groups. These top pulmonary researchers are working together to combat respiratory disease through translational research. DZL scientists are located at 24 premier research institutions throughout Germany, and their activities are 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, end-stage 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 are applied to the 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 cross-fertilization of ideas and findings across research areas.

# Asthma and Allergy

| | |
|---|---|
| Disease Area Leaders | Prof. Dr. Heinz Fehrenbach (ARCN) |
| | Prof. Dr. Dr. h.c. Erika von Mutius (CPC-M) |
| Participating DZL Partner Sites | All |

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 very similar (e.g. wheezing, shortness of breath, and coughing), population-based clinical and genetic studies suggest that asthma is not just one disease but many. Thus, a single "one-size-fits-all" treatment approach is unlikely to succeed in tackling this important health problem. In order to design personalized treatment approaches for asthma patients, there is an urgent need to elucidate the molecular 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.




The Disease Area Asthma and Allergy with its core areas of cooperative research projects combines basic research with clinical research.

## Goals for 2015

**Goal 1 – German Collaborative Asthma Cohort**

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

**Goal 2 – Mechanisms Underlying the Development of Asthma Phenotypes**

- Translational models of asthma phenotypes
  - › Establishment of novel phenotype-specific mouse 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 (EMTU) 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, chip cytometry)
  - › 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 the asthma cohort
  - › Analysis of epigenetic signatures (in particular chromatin modifications) in human BAL and blood samples from an asthma cohort
  - › Establishment and use of a systems biology platform

## Research Highlight 2015

# New drug alleviates symptoms of allergic asthma

Wheezing, coughing and shortness of breath: According to an estimation by the World Health Organization, about 300 million people worldwide suffer from these characteristic symptoms of asthma. Half of all asthmatics are affected by allergic asthma of the so-called Th2 endotype. If a patient comes into contact with the provoking allergen, mast cells in the airways are activated which induce airway constriction. Moreover, interleukins such as IL-4, -5 and -13 are secreted. They trigger inflammation in the lung by recruiting and activating specialized immune cells, the so-called eosinophile granulocytes. In this second, late reaction too, characteristic symptoms of asthma such as impaired lung function and dyspnea are seen. Depending on the severity of the disease, different therapies are available. They can be used in the case of an acute attack as well as for permanent application which leads to a reduction of the risk of an asthma attack.

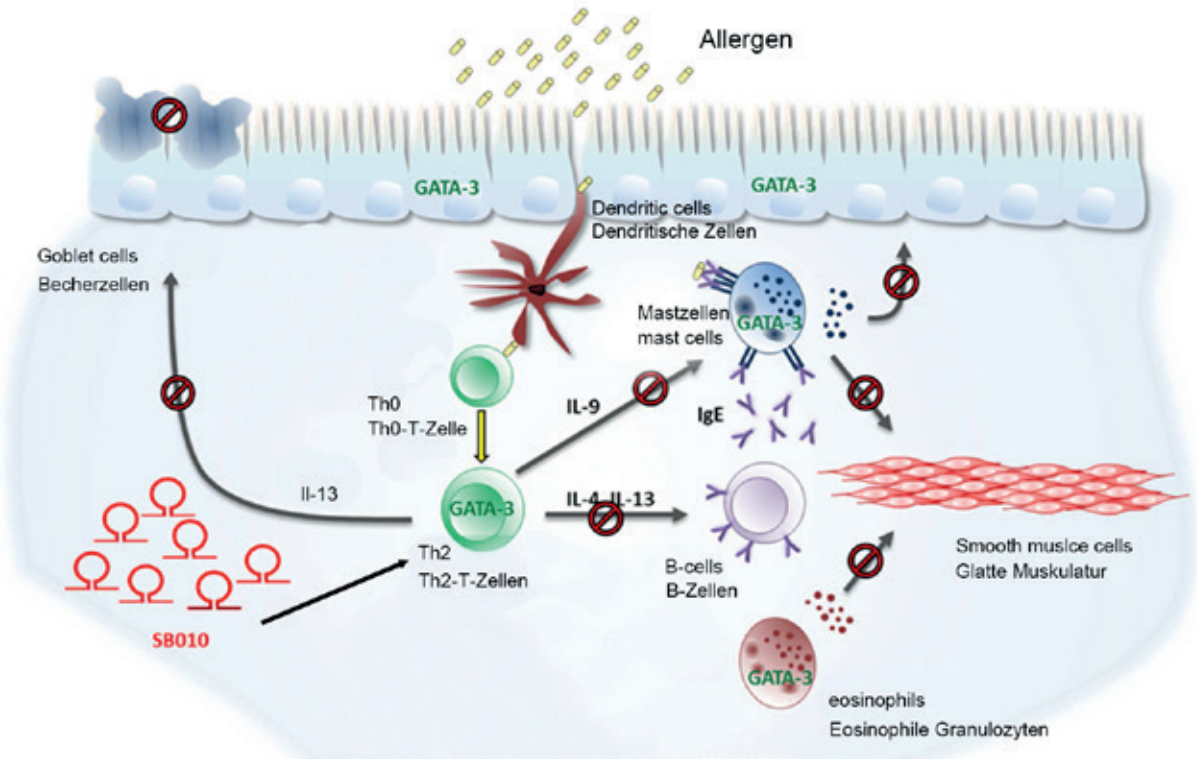
A new strategy aiming for an alleviation of asthma symptoms has been developed by scientists of the DZL sites BREATH and UGMLC in collaboration with Sterna Biologicals. Their concept is based on the finding that the production of the aforementioned interleukins is started only after activation by the so-called transcription factor GATA3. The rationale was now to disable the production of GATA3 and therefore suspend the cascade via interleukins and eosinophil granulocytes. The newly developed drug SB010 showed promising effects in various model systems from cell culture to animal models: SB010 is a so-called DNAzyme which penetrates the cell membrane, specifically destroying the RNA of GATA3 and thus disabling the production of the transcription factor. Based on these experiments, the drug was tested in a clinical trial with 40 subjects suffering from mild allergic asthma. In the meantime, the study has been completed and published in The New England Journal of Medicine in 2015.

Participants of the study inhaled the drug SB010 once a day over a period of four weeks. Afterwards, scientists checked whether there was a change in the severity of the symptoms. To that end, patients were provoked with an allergen in order to induce an asthma attack. This was done under medical supervision. Lung function testing demonstrated an improvement of 11% in the early phase and even 34% in the later phase of an attack. As predicted, the concentration of IL-5 in the blood serum was also significantly decreased. A placebo had no such influence.

Further studies are planned in order to clarify whether SB010 is also effective in severe asthma, and whether it has additional benefit compared to the established standard therapy with inhaled steroids. It may be that SB010 can particularly be of use in cases in which inhaled steroids fail or are ineffective. In addition to that, a larger group of patients should be studied in order to detect possible very rare side effects.

**Further information:**

Krug N, Hohlfeld JM, Kirsten AM, Kornmann O, Beeh KM, Kappeler D, Korn S, Ignatenko S, Timmer W, Rogon C, Zeitvogel J, Zhang N, Bille J, Homburg U, Turowska A, Bachert C, Werfel T, Buhl R, Renz J, Garn H, Renz H. Allergen-induced asthmatic responses modified by a GATA3-specific DNAzyme. The New England Journal of Medicine. 2015, 372:1987-1995.

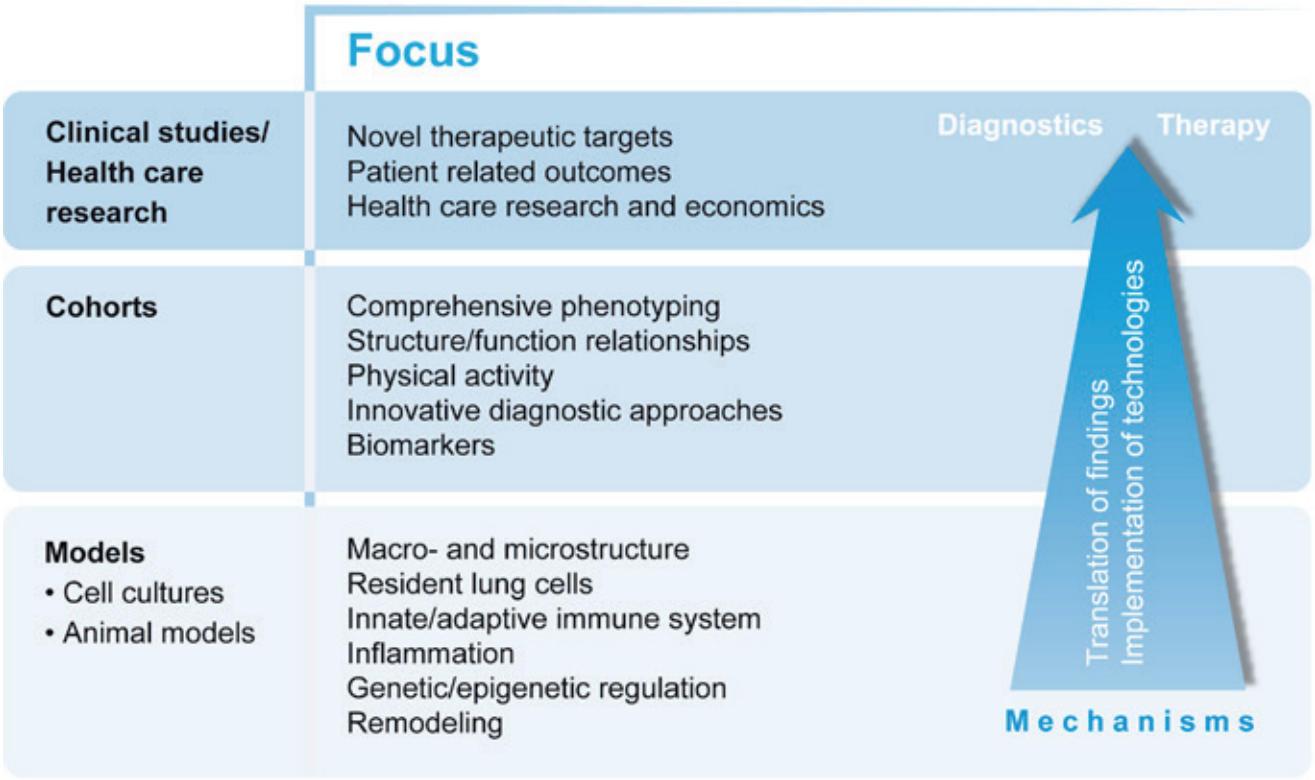



The active substance SB010 facilitates a novel treatment of the most common form of bronchial asthma, the Th2 endotype. Without treatment, those affected suffer from wheezing, coughing and shortness of breath after contact with the provoking allergen.

# Chronic Obstructive Pulmonary Disease (COPD)

| | |
|---|---|
| Disease Area Leaders | Prof. Dr. Klaus F. Rabe (ARCN) |
| | Prof. Dr. Claus F. Vogelmeier (UGMLC) |
| Participating DZL Partner Sites | All |

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 to a certain extent 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 COPD research effort at the DZL is the translation of novel mechanism-based therapeutic concepts into effective therapies for COPD patients.




In the Disease Area Chronic Obstructive Pulmonary Disease, the research focus is on translation of research results and development of new technologies.

## Goals for 2015

**Goal 1 – Remodeling, regeneration and repair: from animal models to human tissuesamples**

- 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 cell cultures from COPD patients
- 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
  - › Standardized collection of volatile organic compounds (VOCs) in patients with COPD severity GOLD I – IV
  - › Validation of the identified factors and development of an algorithm for the diagnosis of COPD
  - › Independent review of the 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 magnetic resonance imaging (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 patient biosamples (sputum, BAL = bronchoalveolar lavage)
  - › 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 industrial partners
- Implementation of Investigator Initiated Trials after approval by the DZL Clinical Trial Board

**Goal 5 – Healthcare management and healthcare economics**

- Finalization of the first data collection (data extraction, data preparation, allocation and feedback to the medical offices)
- Evaluation of collected data (including estimation of reference values for further applications, e. g. reparameterization of the COPD model)

## Research Highlight 2015

# Sports and physical activity can break the downward spiral of COPD

For a long time, physicians told COPD patients that they should rest in order to improve their symptoms, but now it is becoming more and more evident that physical activity and sports have a rather positive influence on the course of the disease.

Scientists from the DZL sites ARCN and BREATH performed the first systematic time-course analysis of the correlation between physical activity and relevant factors of COPD. Results of the study were published in the American Journal of Respiratory and Critical Care Medicine. While earlier analyses were restricted to one time point, researchers of the Lungen-Clinic Grosshansdorf and colleagues from Hannover observed their patients for three years. They used wristband accelerometers to measure the daily activity of the study subjects. The main result is that physical activity – independent of the initial degree of severity – worsens substantially during the course of the disease. Whilst healthy people lose 200 steps per day every year to activity, COPD patients lose on average 400. Concomitantly with physical activity, their lung function and quality of life decrease. Interestingly, muscle mass and exercise intolerance – a decreased ability to perform physical exercise – do not change significantly in comparison to healthy subjects of the same age. Only when patients are permanently and almost completely physically inactive, does their exercise intolerance increase and muscle mass is lost. This result constitutes a starting point for a therapy that can break the downward spiral, often observed by clinicians: before COPD patients reach the point where they become so restricted that they can no longer perform physical exercise, they should become physically active and do as much sport as possible. These new results will soon become part of the German COPD guidelines, so that all patients may benefit from them in their clinical care.

Further investigations of the physical activity of COPD patients during the course of the disease are being pursued at present in a collaborative project between the DZL and COSYCONET (German COPD and Systemic Consequences - Comorbidities Network). The study aims to observe patients for an even longer period of time and take so-called comorbidities into account. Ultimately, COPD is not just a respiratory disease, but it has systemic consequences, for example for the cardiovascular system or – as shown here – for muscle mass.

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**Further information:**

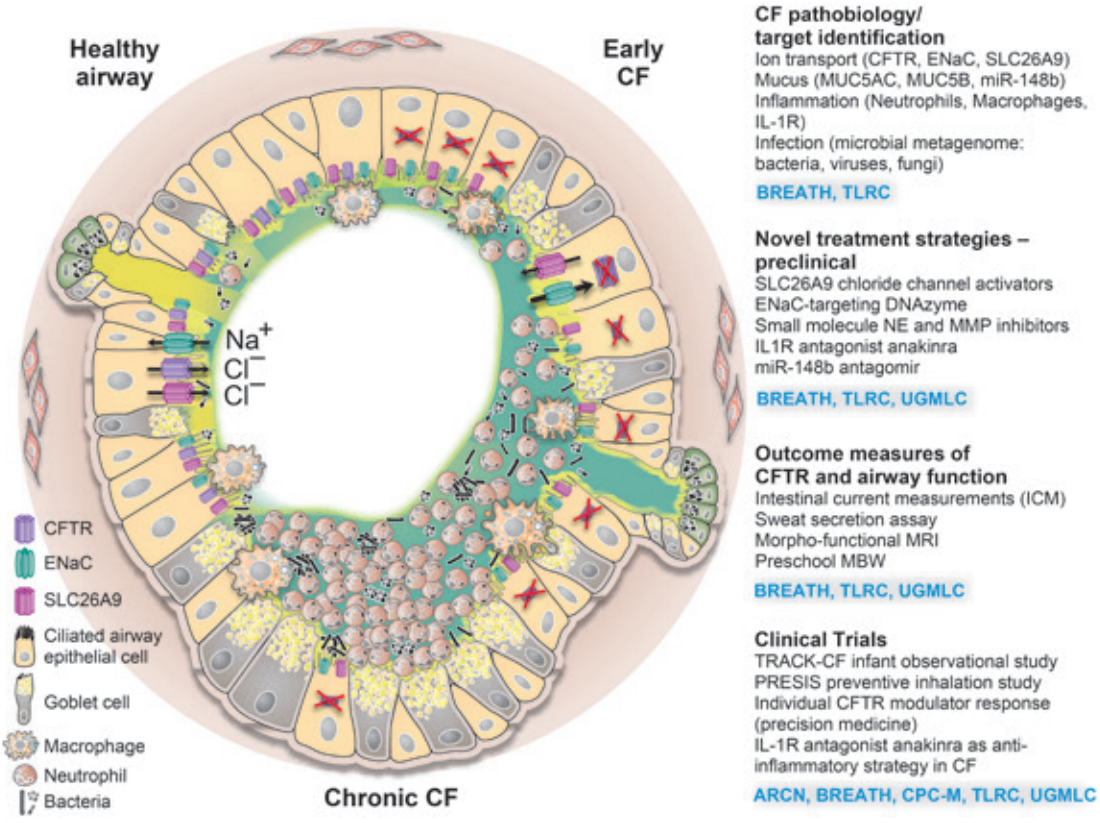
Waschki B, Kirsten AM, Holz O, Mueller KC, Schaper M, Sack AL, Meyer T, Rabe KF, Magnussen H, Watz H. Disease Progression and Changes in Physical Activity in Patients with Chronic Obstructive Pulmonary Disease. American Journal of Respiratory and Critical Care Medicine. 2015, 192:295-306.

Lung function measurements contribute to the diagnosis of a COPD.

# Cystic Fibrosis

| | |
|---|---|
| Disease Area Leaders | Prof. Dr. Marcus Mall (TLRC) |
| | Prof. Dr. Dr. Burkhard Tümmler (BREATH) |
| Participating DZL Partner Sites | ARCN, BREATH, TLRC, UGMLC |

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 Germany. With improvements in symptomatic therapies and standardized CF medical care, the median survival age of CF patients in Germany has risen to approximately 40 years. However, despite recent breakthroughs in disease-modifying therapies for a small subgroup of patients with specific CF genotypes, there are currently no therapies available to the majority of patients that target CF lung disease at its root. 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 the effective prevention and therapy of CF lung disease.




Hereditary cystic fibrosis with fatal outcome has up to now only been etiologically treatable in a small number of patients with a specific alteration in the CFTR gene. The translational approach of this Disease Area to combat cystic fibrosis thus involves the identification of possible target structures for therapies, the development of new treatment strategies and testing them in clinical studies.

## Goals for 2015

**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 selected 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
  - › Development of computer models to quantify the influence of epigenetic changes on the course of CF
- Preclinical evaluation of new mucolytic and anti-inflammatory treatment strategies in a mouse model for CF lung disease
  - › Preclinical evaluation of DNAzymes to correct the ion transport defect in βENaC-overexpressing mice
  - › Preclinical evaluation of new anti-inflammatory strategies in βENaC-overexpressing mice

**Goal 2 – Translational CF research: biomarkers and outcome measures**

- Monitoring CFTR (cystic fibrosis transmembrane conductance regulator) function ex vivo and in vivo
  - › Evaluation and use of the CFTR analysis (nPD, ICM and CFTR immunoblots) to improve CF diagnosis
  - › Evaluation and use of CFTR analysis (ICM and CFTR immunoblots) for ex vivo testing of novel CFTR modulators
- Morphology and function of the respiratory system: pulmonary magnetic resonance imaging (MRI) and mucociliary clearance
  - › 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 a CF newborn screening cohort
  - › Implementation of lung MRI for CF patients in clinical routine diagnostics at the DZL sites TLRC and BREATH

**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 IIa study for preventative 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 (NGS) before, during and after pulmonary exacerbation
  - › Conducting a prospective clinical study to test the efficacy of antibiotic intervention of the upper airways

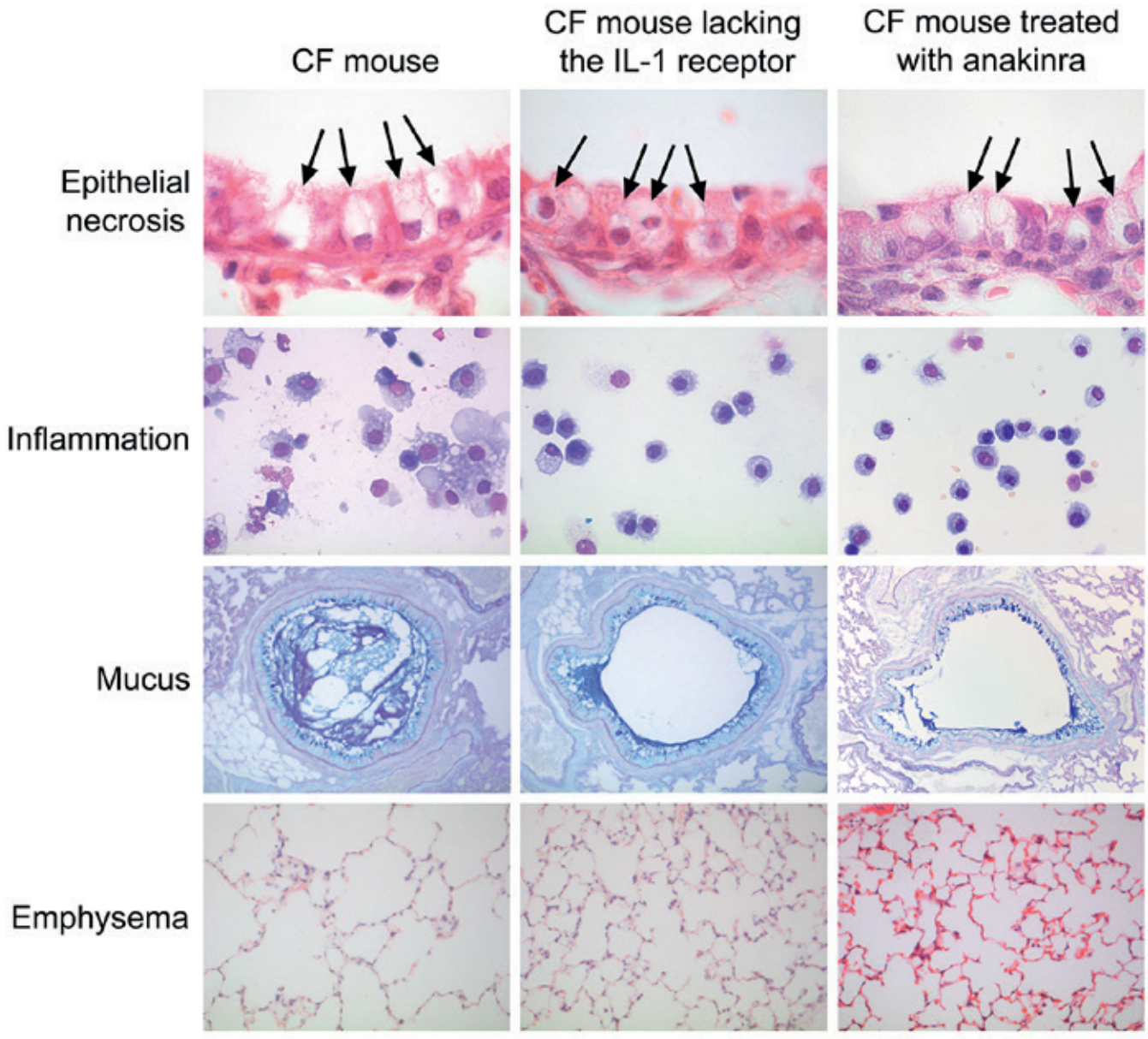
## Research Highlight 2015

# Interleukin-1 receptor inhibition as a novel treatment of chronic airway inflammation in cystic fibrosis

In patients with cystic fibrosis (mucoviscidosis), mutations in the CFTR gene cause an early-onset airway disease characterized by chronic mucus obstruction and airway inflammation starting already in infancy. Chronic airway inflammation plays a key role in progressive lung damage through the release of tissue-damaging factors. This often leads to respiratory failure in early adulthood which remains the most frequent cause of early death in patients with cystic fibrosis. As yet, however, there are no effective drugs to tackle the chronic airway inflammation. DZL scientists and their collaborators in the USA have succeeded in identifying in a mouse model the pro-inflammatory messenger interleukin-1 and its receptor (interleukin-1 receptor) as a new target for anti-inflammatory therapy in cystic fibrosis. Experiments in mice and patients with cystic fibrosis demonstrated that mucus obstruction of the airways causes lack of oxygen, which results in cell death of the airway mucosa. Interleukin-1 released from dying cells activates the interleukin-1 receptor signaling pathway. Studies in mice that lack the interleukin-1 receptor demonstrated that this pathway plays a key role in the development of chronic inflammation in vivo. Following this, the therapeutic efficacy of anakinra, an endogenous antagonist of interleukin-1 receptor, which has already been used successfully in the treatment of rheumatoid arthritis, was investigated. These studies demonstrated that anakinra inhibits chronic airway inflammation almost completely and prevents lung damage in mice with cystic fibrosis-like lung disease. These results in a disease-relevant mouse model (proof-of-concept) present inhibition of the interleukin-1 receptor by anakinra as a promising novel approach for an effective anti-inflammatory therapy in patients with cystic fibrosis. This approach will be tested in an early phase clinical trial in the DZL.

**Further information:**

Fritzsching B, Zhou-Suckow Z, Trojanek JB, Schubert SC, Schatterny J, Hirtz S, Agrawal R, Muley T, Kahn N, Sticht C, Gunkel N, Welte T, Randell SH, Langer F, Schnabel P, Herth FJ, Mall MA. Hypoxic epithelial necrosis triggers neutrophilic inflammation via IL-1 receptor signaling in cystic fibrosis lung disease. American Journal of Respiratory and Critical Care Medicine. 2015, 191:902-913.

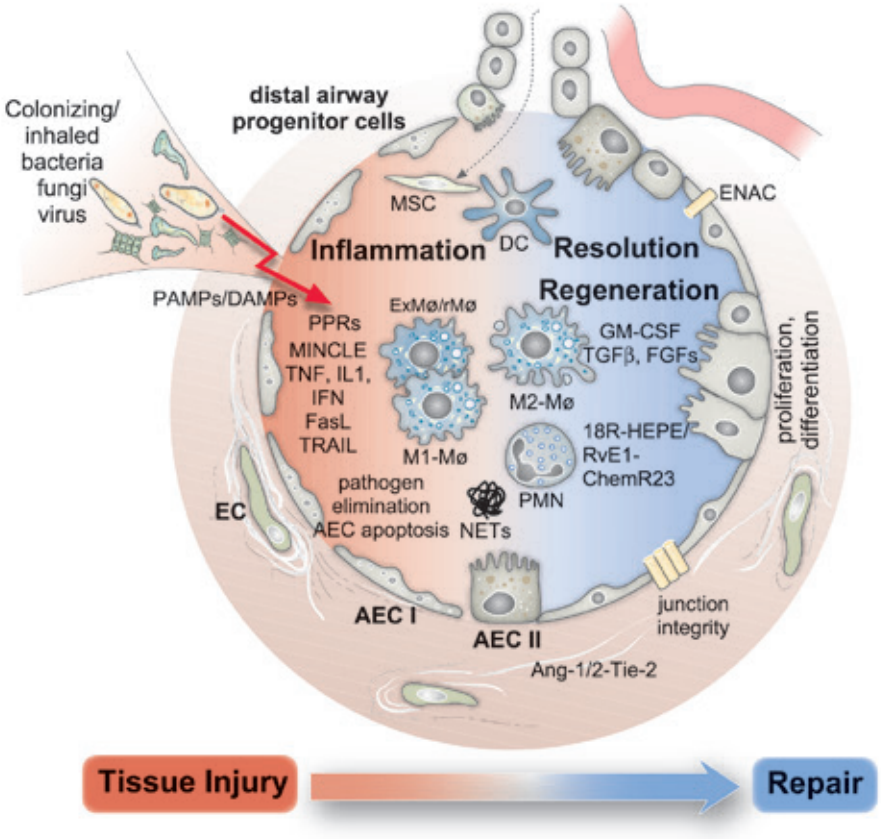



The interleukin-1 receptor is a new therapeutic point of application in the fight against cystic fibrosis - chronic airway inflammation. Mice (CF mouse) and patients with cystic fibrosis develop chronic airway disease characterized by necrosis of the airway mucosa and release of interleukin-1, chronic inflammation, mucus plugging and tissue damage (left column). Genetic deletion ("knock-out") as well as pharmacological inhibition of the interleukin-1 receptor by treatment with the interleukin-1 receptor antagonist anakinra results in a substantial reduction in airway inflammation, mucus plugging and tissue damage (middle and right column). Therefore, inhibition of the interleukin-1 receptor with anakinra is a promising new approach for an effective anti-inflammatory therapy in patients with cystic fibrosis.

# Pneumonia and Acute Lung Injury

| | |
|---|---|
| Disease Area Leaders | Prof. Dr. Jürgen Lohmeyer (UGMLC) |
| | Prof. Dr. Tobias Welte (BREATH) |
| Participating DZL Partner Sites | All |

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 therapeutic 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, inhalation of toxic gases) may cause acute lung injury with severe respiratory failure. The goals of this Disease Area are to decipher the molecular mechanisms underlying the spread of inflammatory events in the alveolar compartments and to understand the cellular and molecular signaling pathways driving resolution of inflammation and repair of alveolar integrity. Based on understanding these events, new targeted therapeutic concepts are being developed to attenuate lung tissue damage and promote organ regeneration in pneumonia and ARDS.




BU The Disease Area Pneumonia and Acute Lung Injury aims to understand the mechanisms of emergence and dissolution of inflammation of the alveoli and thus develop novel therapeutic concepts.

## Goals for 2015

**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
  - › Reversal of immune escape strategies of pulmonary pathogens
- Clinical Research
  - › Creation of BAL inflammatory profiles in pneumonia/ARDS patient cohorts

**Goal 2 - Innate Immune Responses in the Lungs**

- Basic Research
  - › 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**

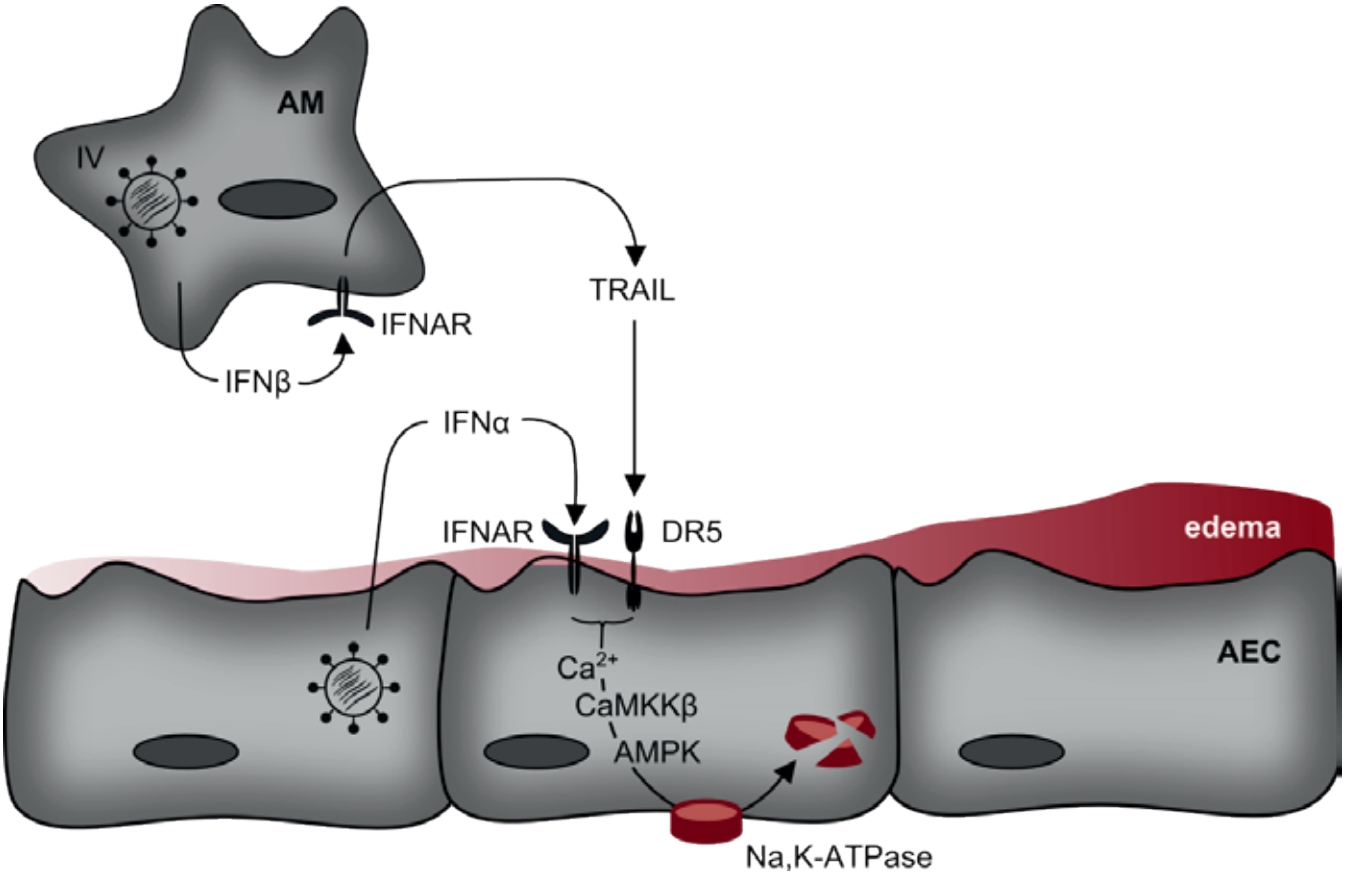
- Basic Research
  - › Investigation of the influence of the pulmonary inflammation processes by local hypoxia, endocrine signals and the type of ion transport
  - › Establishment of intervention strategies to restore damaged inflammatory ion transport and improve endothelial and epithelial barrier function
- Translational Research
  - › Review of pathogenetic relevance of identified candidate molecules by knockout and inhibitor experiments in S. pneumoniae-induced lung injury mouse models
  - › 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**

- Validation of the role of basophil function in strengthening the secondary immune response to intact pneumococcal protein antigens in mice
- Establishment of cell culture systems for the characterization of human basophils against S. pneumonia

## Research Highlight 2015

### Alveolar fluid clearance is impaired after influenza virus (IV) infection by signaling of epithelial type I IFN and macrophage TRAIL




The probability of survival of patients with acute lung failure depends on how well the superfluous fluid from an alveolar edema can be transported away. Researchers of the Disease Area Pneumonia and Acute Lung Injury detected the basic signal pathways and thus opened up possibilities for novel therapies.

Influenza A viruses (IAV) cause primary viral pneumonia resulting in acute respiratory distress syndrome (ARDS) associated with severe alveolar edema formation. As impairment of edema resolution in ARDS patients is correlated with high mortality, this study investigated metabolism and function of Na,K-ATPase, a major regulator of fluid homeostasis, to define mechanisms affecting alveolar fluid clearance (AFC) in IAV infection.

In vivo IAV infection of wild-type (wt) mice resulted in reduced AFC, edema formation and hypoxia that occurred in parallel with a decrease in total and plasma membrane ex-

pressed Na,K-ATPase α1 subunit (NKAα1). NKAα1 was primarily decreased in non-infected cells in a monoculture of alveolar epithelial cells (AEC) and in presence of co-cultured, infected macrophages. We found paracrine signaling of type I interferons (IFN) and the macrophage released, IFN-dependent cytokine TRAIL (TNF-related apoptosis inducing ligand) to be sufficient to decrease NKAα1 in a CaMKKβ- and AMPK-dependent way. Blockade of this pathway using specific chemical inhibitors, adenoviral overexpression or siRNA approaches restored NKAα1 levels as well as vectorial water transport in ex vivo infected AEC. Additionally, trail-/- or ifnar-/- mice, mice transduced with a dominant-negative form of AMPK or ccr2-/- mice lacking pulmonary macrophage recruitment showed improved NKAα1 levels and AFC after IAV infection. In parallel, inhibition of Na,K-ATPase channel activity by ouabain reduced the amount of IAV infected cells, implying a role for Na,K-ATPase in the IAV replication cycle. IAV infection or transfection of the viral M segment led to a mistargeting of NKAα1 from the basolateral to the apical cell surface in infected AEC, associated with a close interaction between the viral M2 protein and the NKAα1, likely resulting in impaired or even reverted fluid clearance in the infected fraction of AEC.

Together, this work demonstrates that AFC is inhibited after IAV infection both in infected cells by M2-mediated mistargeting and in non-infected neighboring cells by paracrine IFN/TRAIL/DR5 signaling, resulting in AMPK-mediated decrease of plasma membrane NKAα1. Targeting these pathways may be a novel therapeutic strategy to improve AFC, oxygenation and, finally, outcome in patients with IAV-induced ARDS.

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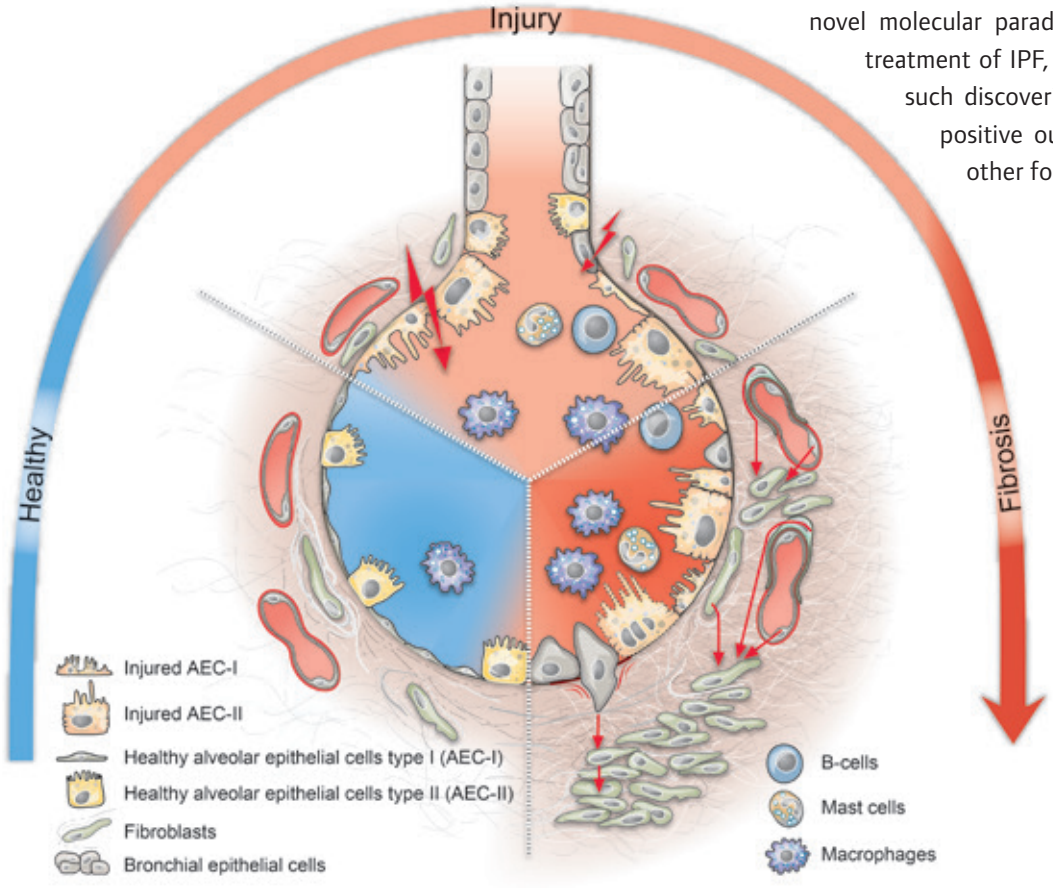
**Further information:**

Peteranderl C, Morales-Nebreda L, Selvakumar B, Lecuona E, Vadász I, Morty RE, Schmoldt C, Bespalowa J, Wolff T, Pleschka S, Mayer K, Gattenloehner S, Fink L, Lohmeyer J, Seeger W, Sznajder JI, Mutlu GM, Budinger GR, Herold S. Macrophage-epithelial paracrine crosstalk inhibits lung edema clearance during influenza infection. Journal of Clinical Investigation. 2016, 126(4):1566-80.

# 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 |

Diffuse parenchymal lung diseases (DPLD) comprise more than 200 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, mechanical 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 focuses primarily 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.




Fibrotic alterations in a DPLD can occur as a result of an acute or chronic lung injury – triggered by chemotherapy, inhalation of toxins, collagen vascular diseases, mechanical ventilation or without known cause.

## Goals for 2015

**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**

- Elucidation of the subcellular distribution and binding partners of Hermansky-Pudlak syndrome gene products
- Effect of cell type-specific marker genes on mRNA and protein concentrations

**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 (WISP-1) bioassays as a diagnostic biomarker for DPLD
- Identification of critical cell type-specific components of 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 interstitial pulmonary disease (IPD) and bronchopulmonary dysplasia (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**

- Elucidation of the influence of pulmonary fibrosis on the clearance of pathogens from the lungs
- 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 bronchoalveolar stem cells
- Evaluation of the suitability of fibrocytes as predictive biomarkers in DPLD
- Identification and characterization of appropriate cell populations for stem cell treatment; assessment of optimal application strategies

## Research Highlight 2015

### How the lung repairs its wounds

Our lungs are permanently exposed to harmful environmental factors that can damage or even destroy their cells. Inhaled toxic particles, bacterial or viral infections, as well as chronic inflammatory responses lead to damaged cells in the lung alveoli that are normally repaired by tissue repair mechanisms. Misdirected or constricted repair mechanisms (e.g. due to aging) may lead to the development of chronic lung diseases such as idiopathic pulmonary fibrosis (IPF).

Up to now there is no causal therapy for IPF. It is known that IPF affects the pulmonary interstitium, the connective tissue between the lung alveoli, especially in the lower parts of the lung. Connective tissue accumulates, the lung tissue hardens and becomes scarred which affects lung compliance. The patients show worsening of lung function and their life quality is significantly limited. The prognosis is poor for IPF patients; the survival rate for most patients is 2-3 years after diagnosis.

DZL scientists, in collaboration with colleagues from the Max Planck Institute (MPI) of Biochemistry in Munich, have now gained detailed insights into the processes regulating matrix and cell turnover in lung injury and fibrosis. Using novel mass spectrometry techniques, the interdisciplinary team of scientists have succeeded, for the first time, to quantitatively analyze and profile dynamic changes in the composition of the lung tissue throughout the inflammatory and regenerative phases.

When the pulmonary alveoli are damaged, various proteins are secreted into the extracellular space, where they form the so-called extracellular matrix (ECM). These proteins are crucial for tissue healing by instructing various processes, including the activation of specific stem cell populations, ensuring that lung tissue can be restored to its original condition. Using mass spectrometry, the scientists have now succeeded for the first time in identifying and quantifying the abundance and solubility of more than 8,000 proteins in the lung proteome throughout the multistage tissue repair processes.

The information gained about the dynamic changes in ECM composition and its interactions with various secreted growth factor proteins will enable the researchers to develop new hypotheses and research approaches for the activation of stem cells in the lung. These novel mass spectrometry techniques will also enable the scientists to analyze variations in the type and abundance of proteins in patients with lung fibrosis and healthy individuals and the results gained from this research will provide an important basis for further basic research on the development of IPF and chronic lung diseases in general, leading to new therapeutic approaches for their treatment.

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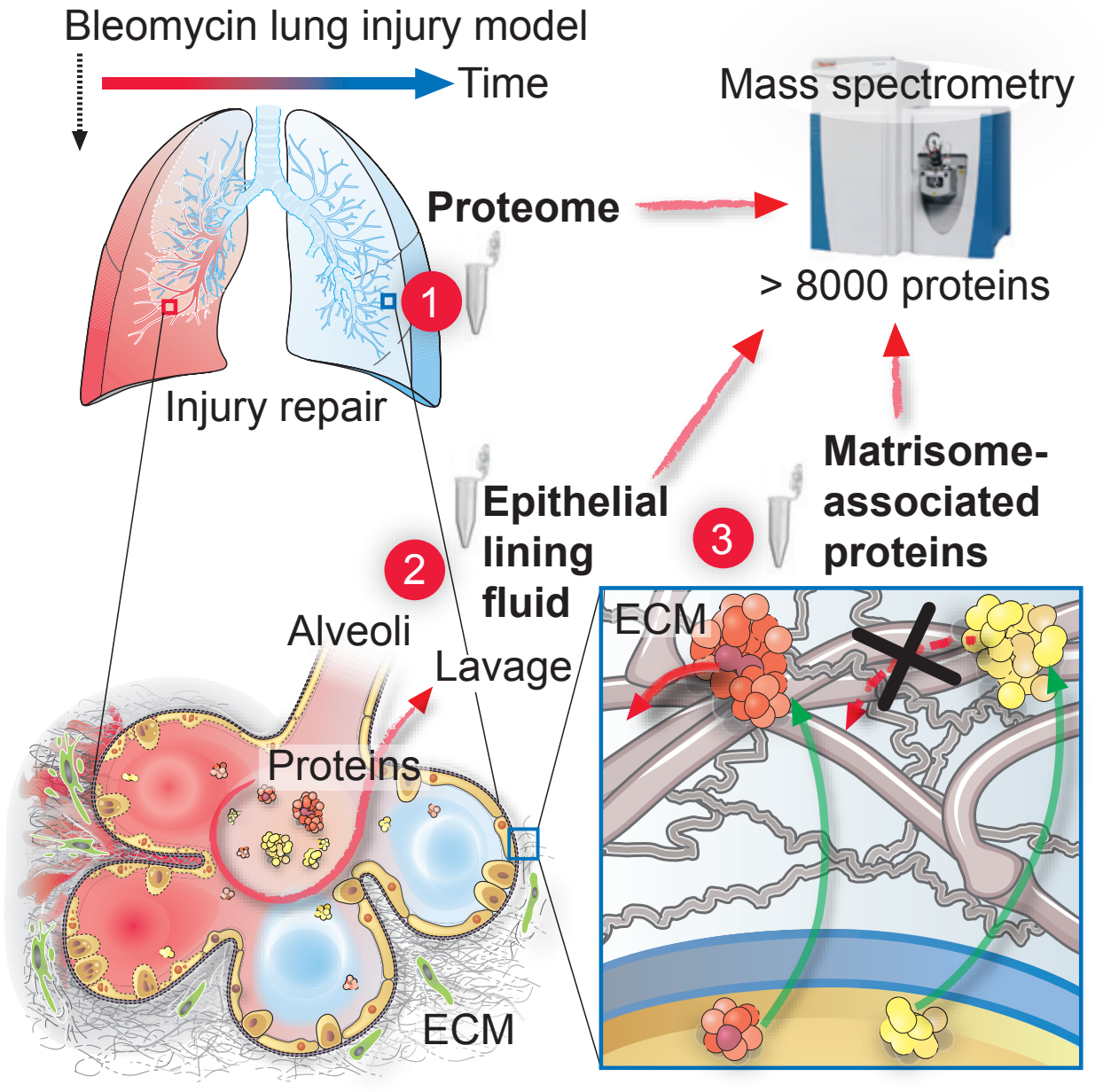
**Further information:**

Schiller HB, Fernandez IE, Burgstaller G, Schaab C, Scheltema RA, Schwarzmayr T, Strom TM, Eickelberg O, Mann M. Time- and compartment-resolved proteome profiling of the extracellular niche in lung injury and repair. Molecular Systems Biology. 2015, 11(7):819.

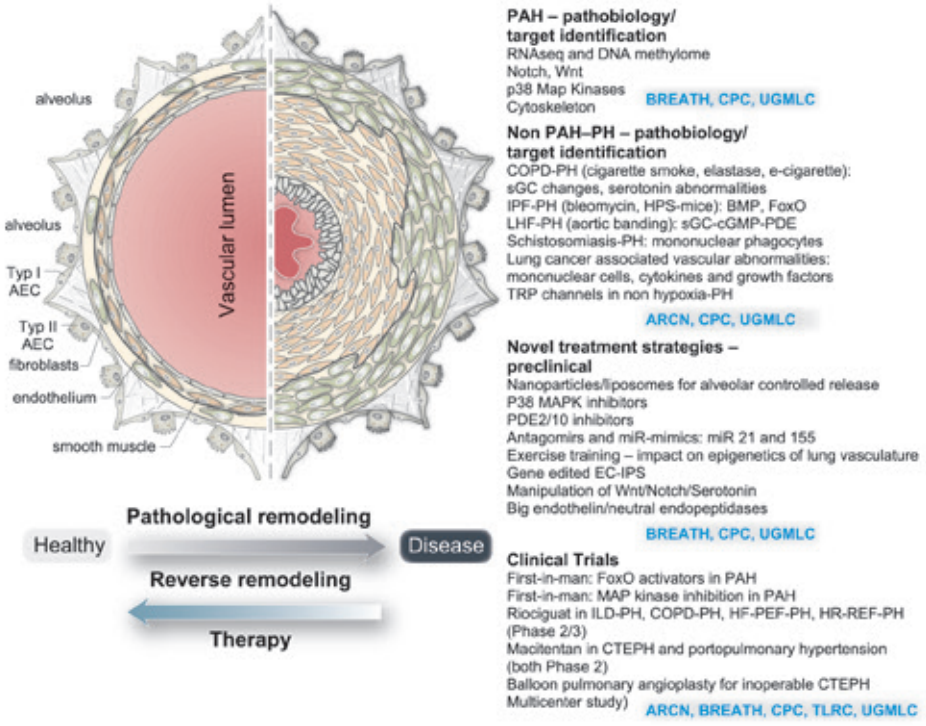



Researchers of the Disease Area Diffuse Parenchymal (interstitial) Lung Disease have succeeded for the first time in presenting dynamic changes in the composition of lung tissue during the inflammation phase and regeneration in idiopathic pulmonary fibrosis (IPF) with the aid of novel methods of mass spectrometry. The DZL scientists have thus provided a possible basis for completely new therapeutic approaches for chronic pulmonary diseases.

# Pulmonary Hypertension

| | |
|---|---|
| Disease Area Leaders | Prof. Dr. H. Ardeschir Ghofrani (UGMLC) |
| | Prof. Dr. Ralph T. Schermuly (UGMLC) |
| Participating DZL Partner Sites | All |

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 about 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, in vascular pruning, and a concomitant increase in right ventricular afterload. Current PH therapy provides symptomatic relief and improves prognosis, but falls short as to the reestablishment of structural and functional lung vascular integrity, as a basis for symptom-free long-term survival. The restoration of physiological vascular structure and function (reverse remodeling) represents the major therapeutic goal of the DZL PH team.




The Disease Area Lung Hypertension focuses on the identification of structures that may serve the purpose of novel therapies. With this knowledge, treatment strategies should be developed in close cooperation between basic research and clinical research and established in clinical studies.

## Goals for 2015

**Goal 1 – Basic Research – From Disease Genes to New Therapeutic Approaches**

- Hypoxia, reactive oxygen species (ROS) signaling pathways and hypoxia-induced gene regulation in PH
  - › Generation of transgenic mice with 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 hypoxia-induced factors (HIFs) using transgenic mice (prolyl hydroxylase, PHD, and Siah ubiquitin ligase)
- New calcium ($Ca^{2+}$) influx pathways in pulmonary hypertension and vascular dysfunction
  - › Investigation of the pathophysiological role of the TRP and the store-operated Orai channels
  - › Investigation of calcium signaling pathways using patch-clamp and single-cell fluorescence imaging in combination with functional studies on endothelial cells and smooth muscle cells
  - › 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

**Goal 2 – Translational Research**

- Promotion of vascular remodeling in PH: transcription factors and receptor tyrosine kinases
  - › Analysis of expression profiles for growth factors in experimental and clinical PH and non-PAH PH
  - › Generation and characterization of a novel transgenic mouse (conditional PDGFR-β knockout mouse)
- Reverse remodeling by the NO-guanylate cyclase-phosphodiesterase (PDE) axis
  - › Examination of expression and activity of various sGC subunits and molecules connected to the signal pathway in experimental and clinical PH and non-PAH PH
  - › Development of inhaled therapy strategies (using 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
  - › Conducting tissue, compartment and cell-specific screens for miRNA profiles in experimental PAH and non-PAH PH models and in human tissue
  - › Identification of promising drug targets and testing their antiproliferative capacity by antagomir treatment in vitro and in preclinical animal models
- Endothelial progenitor cell (EPC)-based revascularization of the lung
  - › 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 (PAB) model

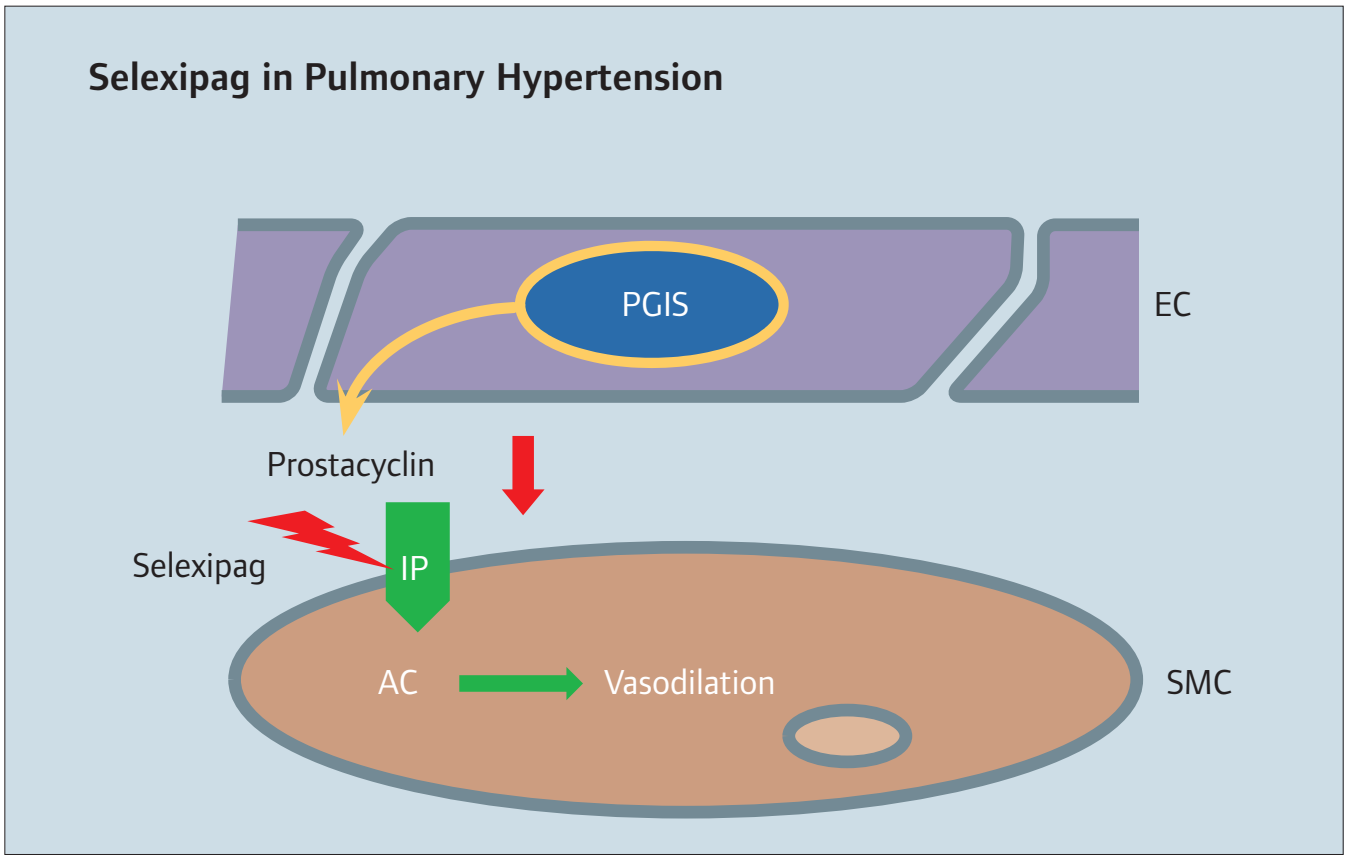
**Goal 3 – Clinical Research**

- Non-hypothesis-based screening for new biomarkers
  - › Examination of tissue from patients with PAH or non-PAH PH compared to healthy individuals
  - › Implementation of broad genome, transcriptome and epigenome analysis screening in lung tissue and 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 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

## Research Highlight 2015

# Innovative prostacyclin IP receptor agonist reduces the risk of a morbidity/ mortality event in patients with pulmonary arterial hypertension

A randomized, multicenter, double-blind, placebo-controlled study involving DZL scientists from the UGMLC and BREATH sites was published in The New England Journal of Medicine, documenting the efficacy of an innovative prostacyclin IP receptor agonist in patients with pulmonary arterial hypertension (PAH). The significance of prostacyclin in PAH therapy is great and is based on the observation that insufficient amounts of this hormone are produced in the pulmonary vessels of affected patients. As a consequence of this observation, in recent years various prostacyclins (and their analogs) have been developed for use in therapy. However, these substances must be administered continuously due to their short half-life, i.e. via prolonged infusion or precisely timed inhalation. In particular, the use of a pump for intravenous prolonged infusion impairs the patients' quality of life enormously and can lead to threatening infections. The development of orally bioavailable substances thus constitutes the logical further development of this form of therapy. The substance selexipag investigated in this study is a selective prostacyclin IP receptor agonist, i.e. it binds to the prostacyclin receptor and leads to vasodilation via an increase in the messenger substance cyclic adenosine monophosphate (cAMP). The long-term efficacy and safety




DZL scientists participated in a successful multinational study to test the long-term efficacy and safety of the drug selexipag. In consequence, the substance is now available for the treatment of pulmonary arterial hypertension.

of orally administered selexipag in this GRIPHON (Prostacyclin (PGI2) Receptor agonist In Pulmonary arterial HypertensiON) study could now be demonstrated.

The study was carried out in 181 centers in 39 countries in North and Latin America, Europe, parts of Asia and in Africa. Many of the patients affected (80%) had already received therapy with other medications (phosphodiesterase inhibitors, endothelin receptor antagonists). In comparison to the placebo, additional administration of selexipag led to a significant reduction in morbidity/mortality events over a period of 3 years. The occurrence of these events was the primary endpoint of the study and was observed in 41.6% of the placebo group but in only 27.0% of those patients treated with selexipag. The side effects of this medication correspond to those of the prostanoids: headaches, sickness and diarrhoea count amongst the most frequently observed side effects.

In summary, due to the positive outcome of this study, selexipag was approved for treatment of PAH in the USA in 2015 and in Europe in 2016. This means that a further medication is now available for the treatment of PAH, a disease that, with an average life expectancy of 3.5 years for patients not receiving therapy, is certainly one of the most serious cardiopulmonary diseases.

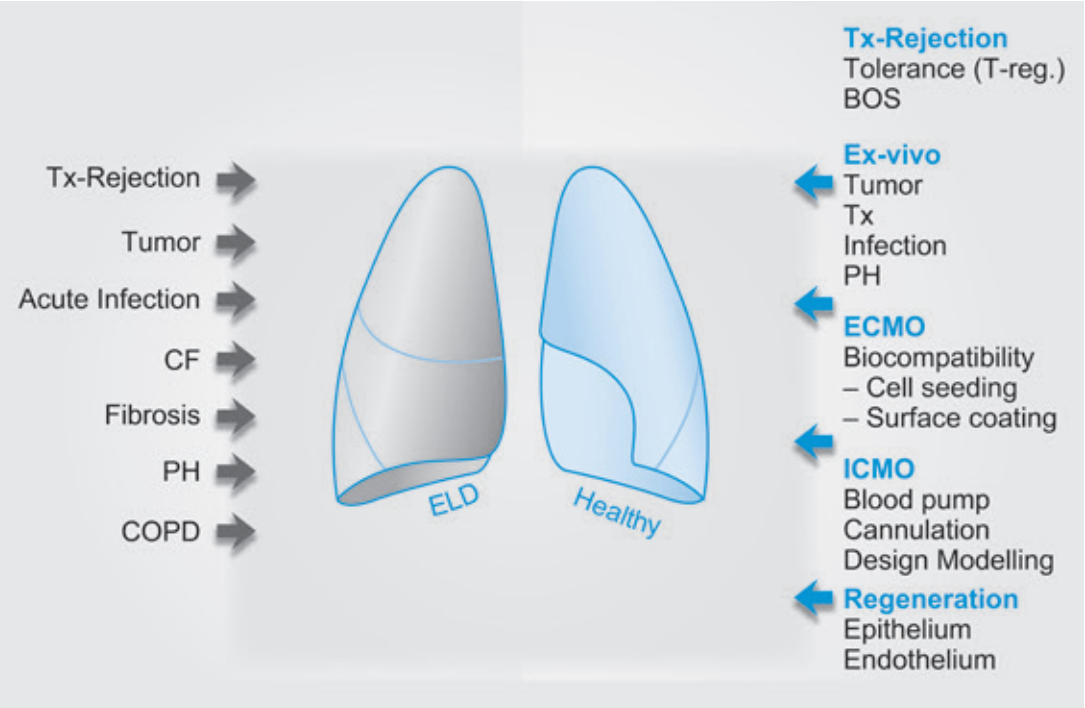
**Further information:**

Sitbon O, Channick R, Chin KM, Frey A, Gaine S, Galiè N, Ghofrani HA, Hoeper MM, Lang IM, Preiss R, Rubin LJ, Di Scala L, Tapson V, Adzerikho I, Liu J, Moiseeva O, Zeng X, Simonneau G, McLaughlin VV, GRIPHON Investigators. Selexipag for the Treatment of Pulmonary Arterial Hypertension. The New England Journal of Medicine. 2015, 373(26):2522-33.

# 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 |

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 membrane 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 diseases (for example, H1N1). In chronic injury, LTx remains the only available therapy with the potential of true long-term survival. LTx, however, is limited only to selected patients, excluding 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 further develop preoperative preparation and postoperative care in lung transplantation to minimize acute and chronic rejection. It also aims to optimize ECMO therapy towards fully implantable lung 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.




Important starting points and aims of the Disease Area End-Stage Lung Disease are the further development of preoperative preparation and postoperative care in lung transplantation (LTx) and extracorporeal membrane oxygenation (ECMO).

## Goals for 2015

**Goal 1 – Lung Transplantation (LTx)**

- Immunology in Lung Transplantation
  - › Immunophenotyping of clinical lung transplant recipients before and after LTx
    - · Monitoring of a regulatory T cell phenotype in peripheral blood mononuclear cells (PBMC) and bronchoalveolar lavage (BAL) after LTx
    - · Individual adaptation of immunosuppression after lung transplantation
  - › Immunological tolerance
    - · Investigation of mechanisms of T cell regulation in a porcine lung transplantation model
    - · Pilot study on administering splenic cells and cytoreduction in the clinical lung transplant program
- 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
    - · Construction of a database and identification of affected patients
    - · Follow-up and identification of a cohort of at least 50 LTx patients with neutrophilic graft dysfunction
    - · Development of new therapeutic strategies in clinical pilot studies
  - › Mechanism of BOS
    - · Identification 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**

- Extracorporeal membrane oxygenation (ECMO) and artificial lung - experimental research
  - › Clinical program (lung failure of various origins)
    - · Development of computerized ECMO simulation
    - · 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
    - · Establishment of a clinical study protocol for the comparison of veno-arterial awake ECMO vs. central interventional lung-assist (iLA) with right heart failure
    - · Conducting a clinical study
    - · Extraction of tissue samples (pulmonary vessels)
    - · Basic research on pulmonary vascular remodeling

**Goal 3 – Regeneration**

- Enothelial induced pluripotent stem cells (iPS) for biohybrid ECMO and PH
  - › Establishment of a protocol for the production of iPS with microvascular EC phenotype

**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

## Research Highlight 2015

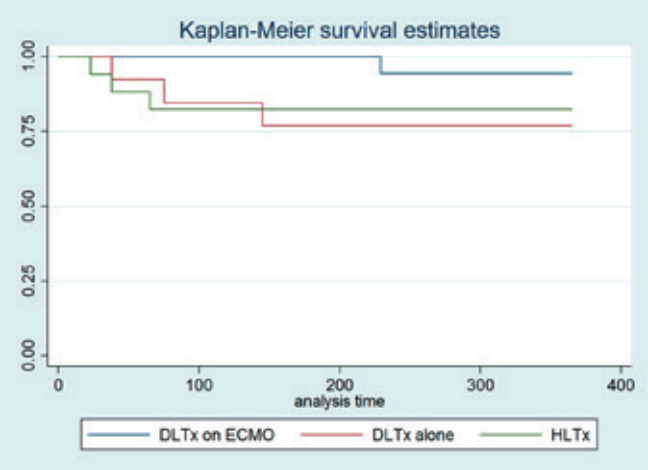
# Lung transplantation for severe pulmonary hypertension--awake extracorporeal membrane oxygenation for postoperative left ventricular remodeling

This publication "Lung transplantation for severe pulmonary hypertension--awake extracorporeal membrane oxygenation for postoperative left ventricular remodelling" represents a profound example of the interdisciplinary work carried out within the disease area "End-Stage Lung Disease" of the German Center for Lung Disease (DZL). Not only does the clinical series reported show the very successful interdisciplinary cooperation between various clinical disciplines involved in the German Center for Lung Disease, but it also exemplifies how the established structures allow for combination of stand-alone technologies for successful application in defined clinical disease entities.

In the work described here, lung transplantation, extracorporeal membrane oxygenation (ECMO) treatment and intensive care unit (ICU) therapies (awake ECMO) were successfully combined, using the established DZL structures at the institution. For the first time ever, a combination of known technologies was applied in patients undergoing bilateral lung transplantation (BLTx) for primary pulmonary hypertension (PH). This innovative approach resulted in a dramatic postoperative improvement in left ventricular cardiac function. The study also shed new light on important pathophysiological phenomena of heart function in PH.

BLTx is an established treatment for end-stage PH. Postoperative ventilator weaning failure, often leads to distinct respiratory deterioration and the need to resume long-term artificial respiration. Thus, these patients have a higher risk of death than those with BLTx for other indications. The scientists involved hypothesized in their paper that left ventricular (LV) dysfunction is the main cause of early postoperative morbidity or mortality and investigated a weaning strategy using awake venoarterial ECMO, thus also temporarily supporting the left ventricular heart function.

In 23 BLTx for severe PH, ECMO used during BLTx was continued for a minimum of 5 days (BLTx-ECMO group). Echocardiography, left atrial (LA) and Swan-Ganz catheters were used for monitoring. Early extubation after transplantation was attempted under continued ECMO.




Researchers from the Disease Area End-Stage Lung Disease, using the innovative combination of known technologies such as extracorporeal membrane oxygenation (ECMO) and awake ECMO, achieved distinct improvements in survival rates after lung transplantation. Many other transplantation groups worldwide have since adopted the novel therapeutic approach with positive results.

Preoperatively, all patients had a severely reduced cardiac index (mean, 2.1 l/min/m2). On postoperative day 2, reduction of ECMO flow resulted in increasing LA and decreasing systemic blood pressure. On the day of ECMO explantation (median, postoperative day 8), LV diameter had increased; LA and blood pressures remained stable. Survival rates at 3 and 12 months were 100% and 96%, respectively. Data were compared to two historic control groups of BLTx without ECMO (BLTx ventilation) or combined heart-lung transplantation for severe PH.

Ultimately, shortly after BLTx for severe PH, the LV may be unable to handle normalized LV preload. This can be effectively bridged with awake venoarterial ECMO. Not only has this interdisciplinary approach of combining various surgical and ICU technologies resulted in significantly improved survival rates of the patients treated, but in a very short period of time, this treatment was adopted by many other transplant groups internationally, confirming our results.

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**Further information:**

Tudorache I, Sommer W, Kühn C, Wiesner O, Hadem J, Fühner T, Ius F, Avsar M, Schwerk N, Böthig D, Gottlieb J, Welte T, Bara C, Haverich A, Hoeper MM, Warnecke G. Lung transplantation for severe pulmonary hypertension--awake extracorporeal membrane oxygenation for postoperative left ventricular remodelling. Transplantation. 2015, 99(2):451-8.

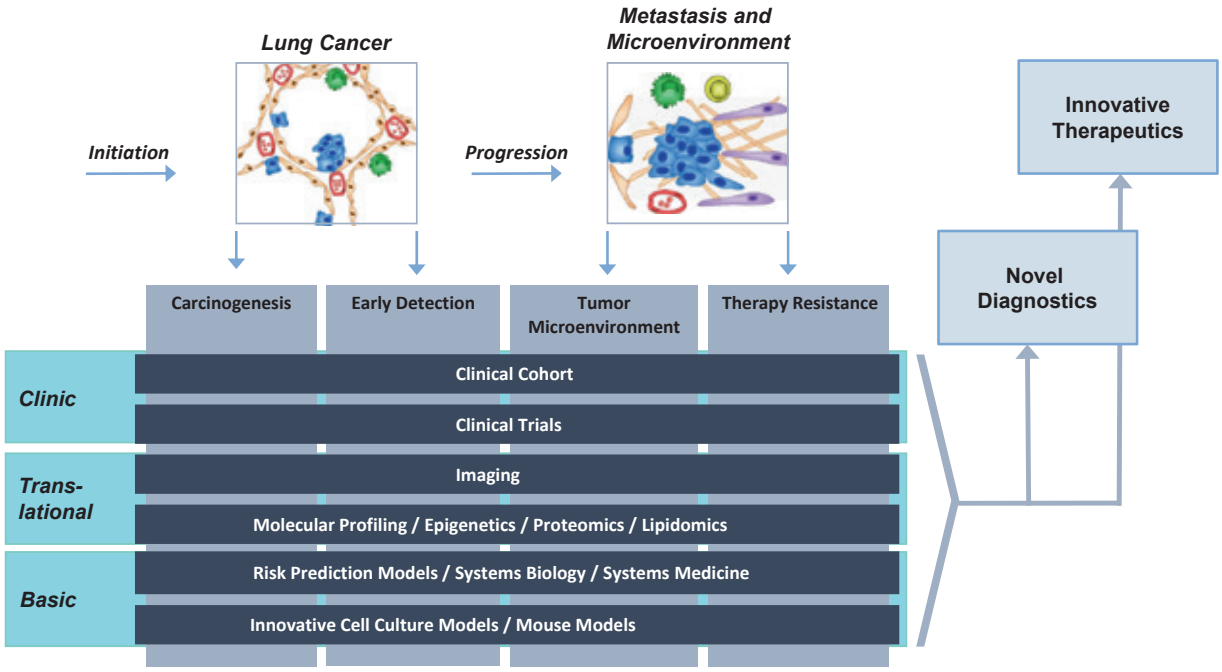
# Lung Cancer

| | |
|---|---|
| Disease Area Leaders | Prof. Dr. Ursula Klingmüller (TLRC) |
| | Prof. Dr. Michael Thomas (TLRC) |
| Participating DZL Partner Sites | All |

Lung cancer is a high incidence and high mortality disease. The two main lung cancer types are small-cell lung cancer (SCLC; 20-30% of cases) and non-small cell lung cancer (NSCLC; 70-80% of cases). Almost 40 % of NSCLC patients present with metastases at time of diagnosis. Advances in molecular profiling have led to new opportunities for developing personalized therapies (precision medicine) that – alone or in combination with surgery, chemotherapy or radiation - will enable application of the most effective treatment regimen for each patient.

Molecular characterization of tumors shows a high heterogeneity in genetic and epigenetic patterns. Oncogenic driver mutations and alterations in gene expression during tumor development greatly impact on the success of therapies and clinical outcome. Due to the limited response to existing targeted therapies, it is crucial to identify markers that are associated with therapy resistance and markers that facilitate stratification of patients according to their predicted therapeutic response.

Our research focuses on the early detection of lung cancer as well as the elucidation of mechanisms that contribute to tumor evolution and therapy resistance with the ultimate goal to advance precision medicine and the development of novel anticancer drugs. Lung cancer research at the DZL is an interdisciplinary and integrative program, exploring clinically well characterized tissue and blood samples with epidemiologic, genetic, epigenetic and systems biology approaches.




The research profile of the Disease Area Lung Cancer combines, in a translational approach, basic research with clinical research to establish novel diagnostic and therapeutic perspectives.

## Goals for 2015

**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 a candidate gene list
  - › Establishment of a lung cancer risk prediction model
- Clinical validation of epigenetic lung cancer markers
  - › Review of the predictive power of epigenetic markers
  - › Validation of the diagnostic capacity of markers for early stages of lung cancer

**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 from 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 in early screening programs
  - › Identification of epigenetic risk factors

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

- Dynamics of signal transduction and cell migration in lung cancer cells
  - › Establishment of 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
  - › Validation of prognosis-determining molecular patterns
  - › Prediction and confirmation of mechanisms driving early metastasis
  - › Construction of 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
  - › Prediction of the effects of treatment combinations in vitro
- Characterization of the early response to systemic and radiation therapy
  - › Analysis of tumor response by morphological and functional imaging
  - › Elucidation of the mechanisms of therapy resistance
  - › Construction of a patient cohort
- Improved treatment options
  - › Development of decision options
  - › Identification of targets for maintenance therapy

**Goal 5 – Strategies to Mitigate Therapy Resistance**

- EGF (epidermal growth factor) 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
  - › Construction of a patient cohort
  - › Validation of the model predictions for developing and overcoming therapy resistance in patient material
  - › Definition of 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

## Research Highlight 2015

# The pregnancy-associated protein glycodelin as a new follow-up biomarker for non-small cell lung cancer (NSCLC)

The glycodelin protein is an important factor during pregnancy as it ensures the successful establishment of immunotolerance between fetus and mother. Besides its function during pregnancy, it has been observed that glycodelin is upregulated in several hormone-regulated tumors. Its role and significance in non-small cell lung cancer (NSCLC) has now been clarified.

Using patient tumor tissue and blood samples from the lung biobank Heidelberg, DZL scientists from Heidelberg investigated the expression of the glycodelin gene in a large cohort of 362 NSCLC patients. In approximately 80% of all NSCLC patients, glycodelin was overexpressed in the tumor compared to the adjacent normal lung tissue (Figure A). Glycodelin was also detectable in the serum of approximately 40% of all NSCLC patients. Importantly, the serum concentration in NSCLC patients was significantly elevated compared to patients with non-malignant chronic obstructive pulmonary disease (COPD) (Figure B). Using serum samples collected during disease follow-up, we found that monitoring the glycodelin serum concentration was a suitable indicator for recurrence of the tumor or metastatic disease (Figure C). Deletion of the glycodelin gene in a cell culture model (knock-out) resulted in elevated levels of programmed death-ligand 1 (PD-L1) and prostaglandin-endoperoxide synthase 2 (PTGS2/COX2) in the cancer cells. PD-L1 suppresses the immune system in the direct vicinity of a tumor and anti-PD-L1 therapies have recently been introduced in the clinical management of lung cancer, to combat the disease by reactivating the immune defense. COX2 fosters formation of new blood vessels, thereby promoting tumor growth.

These findings suggest that glycodelin contributes to the regulation of the immune system in the tumor microenvironment. Therefore, it is planned to examine in further studies whether glycodelin is a new suitable therapeutic target and whether treatment of NSLC patients with anti PD-1/PD-L1 therapy results in an increase in glycodelin production of the tumor. Using follow-up serum samples of patients at late disease stages, it will be investigated whether glycodelin is a suitable early marker for disease progression that may improve disease management by chemotherapy.

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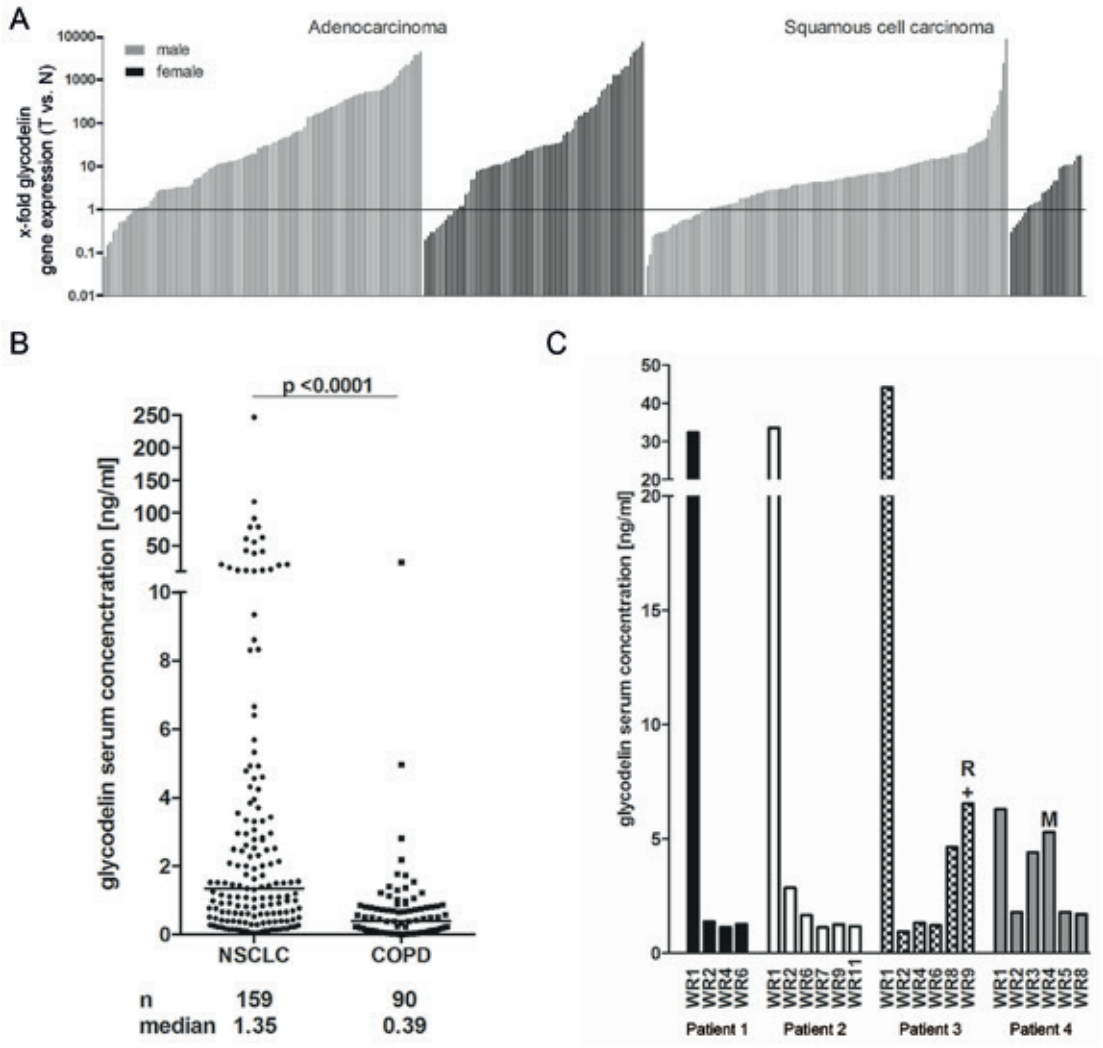
**Further information:**

Schneider MA, Granzow M, Warth A, Schnabel PA, Thomas M, Herth FJF, Dienemann H, Muley T, Meister M. Glycodelin: A new Biomarker with Immunomodulatory Functions in Non-Small Cell Lung Cancer. Clinical Cancer Research. 2015, 21(15):3529-40.




The occurrence of the protein glycodelin is greatly increased in patients with non-small cell lung cancer (NSCLC) and clearly involved in the regulation of the immune system in the tumor microenvironment.

A) The diagram shows the overexpression of the glycodelin gene (indicated by values above 1) in approximately 80 % of 336 investigated lung tumor compared to normal tumor tissue.

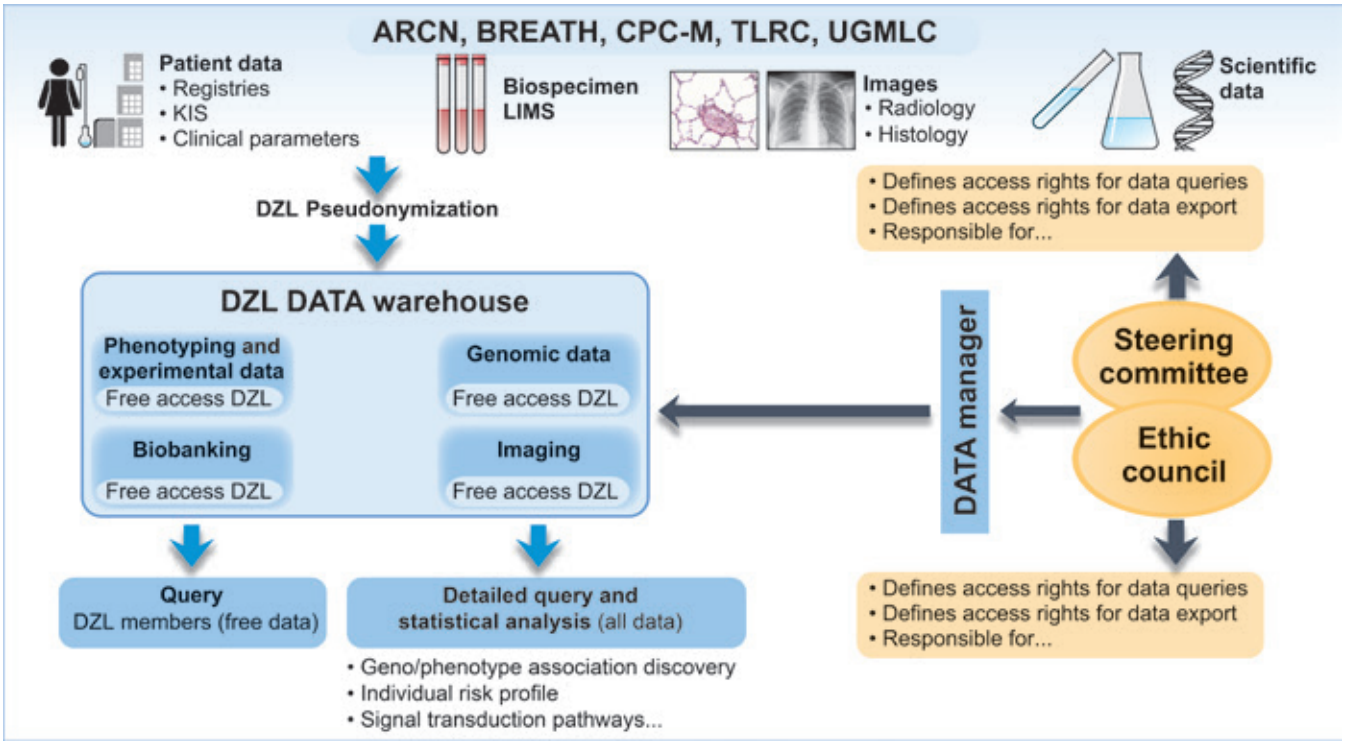
B) Elevated serum concentrations of glycodelin in patients with NSCLC compared to patients with chronic obstructive pulmonary disease (COPD).

C) The diagram depicts the glycodelin concentration in the serum of 4 patients before surgery (WR1) and during follow-up ward rounds. After successful removal of the tumor, glycodelin levels dropped down to a low level for all patients. In the case of recurrence of the primary tumor (R, patient 3) or a new metastasis (M, patient 4), the glycodelin serum levels increased again.

# Biobanking Platform

| | |
|---|---|
| Scientific Coordinators | Prof. Dr. Andreas Günther (UGMLC) |
| | Dr. Thomas Muley (TLRC) |

The DZL Disease Areas are supported by an extensive network of central infrastructure including the Biobanking Platform. The overall aim of the DZL Biobanking Platform is the collection and storage of biospecimens and associated clinical 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.




The core aim of the Biobanking Platform is the establishment of a collection of data and biomaterial for the various pulmonary disease areas, fed and retrievable by DZL scientists and cooperation partners, thereby facilitating center-wide exchange and collaborative research to combat widespread lung disease.

## Goals for 2015

**Goal 1 – Implementation of a DZL Biobanking Portal**

- Regular meetings of the platform´s working groups
- Modular extension of the portal on demand

**Goal 2 – Harmonization of procedures and standards**

- Definition of standards by the DZL Biobanking Working Group, regular meetings
- Harmonization of existing SOPs
- Implementation of new SOPs for harmonized patient consent form, collection of biomaterial, storage and shipping

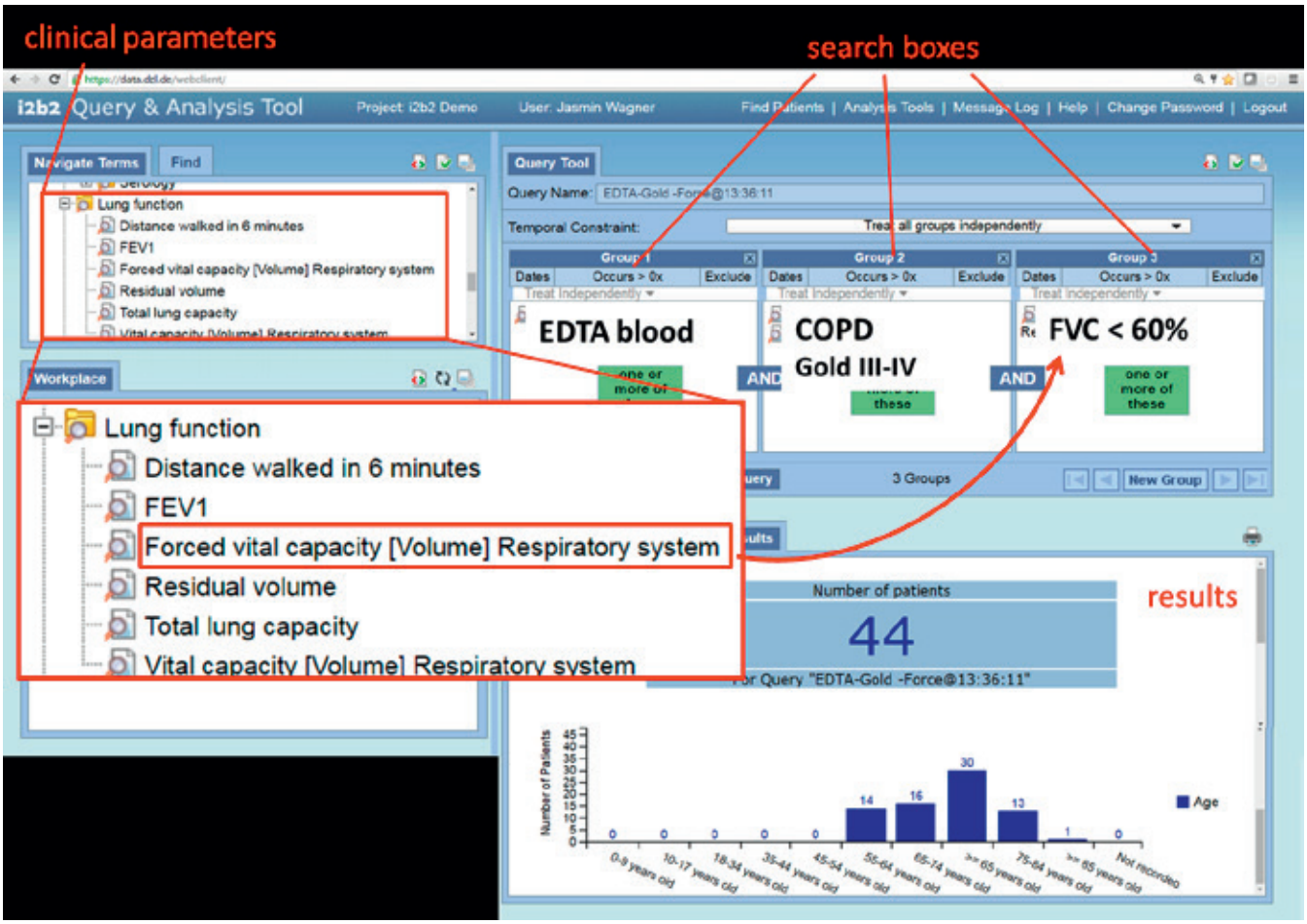
**Goal 3 – Harmonization of phenotyping tools**

- Harmonization of existing phenotyping tools
- Establishment and development of disease-specific phenotyping tools

## Research Highlight 2015

### DZL data warehouse implementation and pilot study in data harmonization

After the establishment of a data safety concept on the basis of the generic TMF recommendations and the decision to use i2b2 (Informatics for Integrating Biology & the Bedside) as an open source solution for the DZL data warehouse implementation, a complex client for data transmission has been developed. In 2015, data sources from four different sites (BioMaterialBank Nord, Lung Cancer Database Heidelberg, Biobank Gauting, European Registry for idiopathic pulmonary fibrosis) have been integrated in the central data warehouse. Already in this test stage, a real world targeted search for various parameters in i2b2 is possible (see Figure). A long-term perspective aim is to include data of all DZL patient registries and cohorts in the data warehouse, for which a continuous data harmonization process will be necessary.




The open source software i2b2 allows DZL researchers to retrieve parameters that are-deposited in the central database on the various lung diseases. Detailed cooperative agreements that regulate the harmonization of the data from the partners' individual source systems form the basis for the deployment of the data.

In a pilot study of data harmonization and integration in the Disease Area Lung Cancer, data from clinical information systems (KIS) of the participating hospitals have been harmonized. The resulting harmonization table contains 285 parameters including tumor-specific parameters (e.g. TNM staging, histology) as well as parameters used across all Disease Areas (e.g. laboratory findings, lung function data). The overall aim of this study is to transfer the different data schema and parameter definitions (e.g. tumor category: T1a, 1A or 11, smoking status: Yes/No, pack years, cigarette/pipe/cigar, etc.) into one i2b2-based database. The study has been published in Methods of Information in Medicine (Firnkorn et al 2015). Now, the project allows the mapping of the entire process starting from the individual KIS through harmonization of the parameters, data import to i2b2, selection of specific cohorts up to the export of selected parameters in common data formats (Excel, CSV). These exported data sets can be further processed with statistical software or data mining tools.

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**Further information:**

Firnkorn D, Ganzinger M, Muley T, Thomas M, Knaup P. A Generic Data Harmonization Process for Cross-linked Research and Network Interaction. Construction and Application for the Lung Cancer Phenotype Database of the German Center for Lung Research. Methods of Information in Medicine. 2015, 54: 455-460.

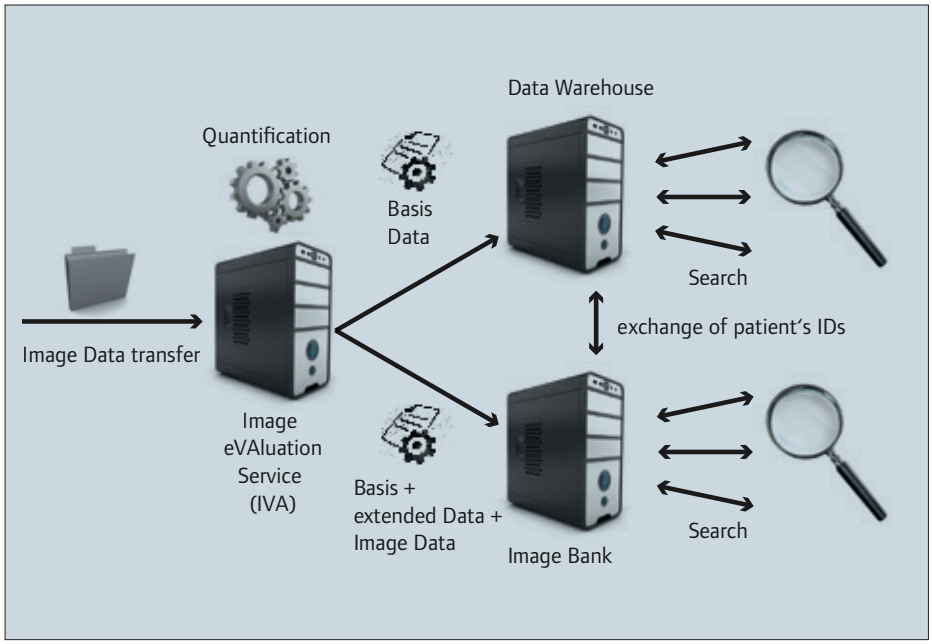
# Imaging Platform

| | |
|---|---|
| Scientific Coordinators | Prof. Dr. Heinz Fehrenbach (ARCN) |
| | Prof. Dr. Hans-Ulrich Kauczor (TLRC) |
| | Prof. Dr. Matthias Ochs (BREATH) |

A wide range of innovative imaging approaches is used in the life sciences to understand living systems and to support the drug discovery processes. The Imaging Platform has been established as a network of complementary expertise and infrastructure within the DZL to ensure scientific exchange and access to cutting-edge imaging technologies in research. Comprising radiology and microscopy, the Imaging Platform aims to identify and benefit from the interfaces between them. The core function of the platform is to offer, disseminate, and share imaging technology. In 2015 the platform has been significantly involved in cross-center activities and prospective multi-center trials. Furthermore, it has underlined the ambition of a close collaboration with the representatives of the Disease Areas by the initiation of its own scientific project "GAVA – Growing and Ageing of Vessels and Airways".

The core project of the Platform is the implementation the Image Bank, a central database which will be linked to the data warehouse of the DZL. The use of this database should comply with the ethical and legal framework, data protection laws and the corresponding body of rules and regulations in operation at the partner sites within the DZL.

The exchange of data between DZL-sites and the Image Bank will be provided by a software solution developed in-house, which is expected to be rolled out to the DZL sites in late 2016. This software will communicate directly with the Image Evaluation Service (Image eVAluation service - IVA) and validate the correct use of pseudonyms according to the DZL guidelines and the SOP published by the Platform Imaging before the actual data transfer is initiated. IVA has been implemented to extract metadata from DICOM files and to provide an automatic quantification of image data with standardized software tools. The quantification results, as well as the image data itself, will be indexed in the Image Bank. The DZL data warehouse only receives the basic data set excluding imaging data.




The core project of the Imaging Platform is the establishment and management of a central imaging database, the Image Bank, that can be fed with data and the data retrieved centerwide by DZL scientists and cooperation partners.

## Goals for 2015

**Goal 1 – Framework**

- Development of the central office and data warehouse
  - › Usage and development of the data warehouse
- Implementation of basic rules
  - › Development of SOPs (standard operating procedures) for the most important imaging procedures
  - › Specification of costs
- Action plan
  - › Development of an action plan for use of imaging in the Disease Areas
  - › Development of strategies for implementation along the translational research chain

**Goal 2 – Radiology**

- Preclinical imaging
  - › Evaluation and usage of specific computer tomography (CT) and magnetic resonance imaging (MRI) techniques
  - › Evaluation and usage of phase contrast imaging
  - › Evaluation and usage of specific techniques for molecular imaging, e.g. position emission tomography (PET)
  - › Evaluation and usage of high resolution sonography
- Translational imaging
  - › Evaluation and usage of specific techniques for proton MRI
  - › Evaluation and usage of non-proton MRI
  - › Evaluation and usage of dedicated tracers (e.g. PET) in inflammation, necrosis and clearance
- Clinical imaging
  - › Evaluation and usage of specific CT techniques
  - › Evaluation and usage of specific MRI techniques
  - › Evaluation and usage of dedicated tracers (PET)

**Goal 3 – Microscopy**

- Optical coherence tomography (OCT)
  - › Establishment of intraoperative OCT
  - › Establishment of OCT in combination with optical projection tomography
- Advanced fluorescence microscopy (AFM)
  - › Establishment and validation of multiplex AFM for molecular imaging
- Multiphoton microscopy
  - › Usage of multiphoton microscopy in combination with OCT
- Electron microscopy and stereology
  - › Establishment and validation of electron microscopy
  - › Establishment and validation of stereology in mouse models of emphysema

## Research Highlight Microscopy 2015

# Alveolar derecruitment and collapse induration as crucial mechanisms in lung injury and fibrosis

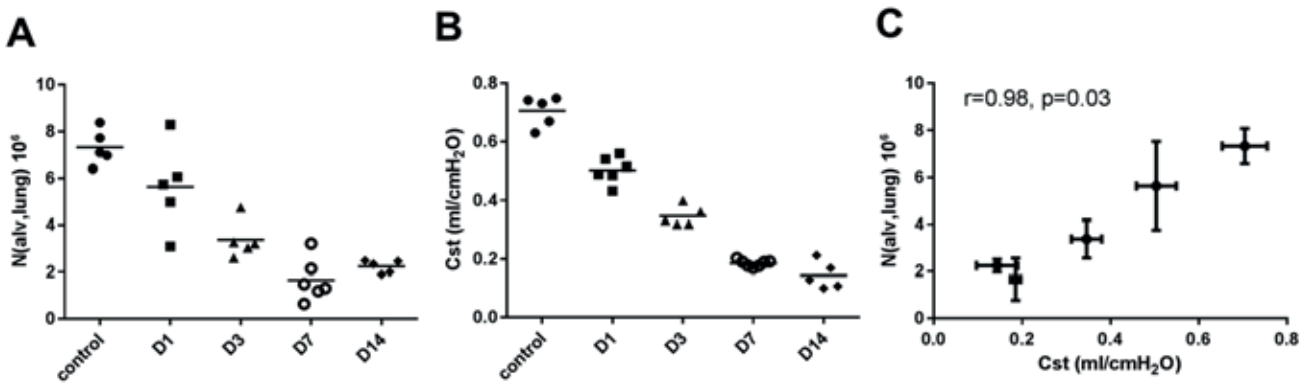



Fig. 1: In an animal model of pulmonary fibrosis, the number of open alveoli (N(al,lung)) and the lung function value (Cst) decrease as the disease progresses. The number of open alveoli correlates with the lung function.

Idiopathic pulmonary fibrosis (IPF) is a rare but fatal disease. A chronic injury of the cells lining the alveoli leads to a progressive scarring. The damaged cell layer contains cells which produce surfactant, a substance that keeps alveoli open. Surfactant function is disturbed in IPF patients. Should this disturbance be already present during the early phase of the disease, alveoli would collapse. The aim of this study was to investigate the causal role of surfactant dysfunction and alveolar collapse in lung injury with scarring. In the bleomycin model of lung fibrosis in the rat, lungs were analysed functionally and by quantitative microscopy during the course of the disease (Fig. 1). Already on day 1, surfactant alterations were present which progressed during the disease. This was accompanied by a decrease in the number of open alveoli on day 3 and day 7. This number remained stable between day 7 and day 14, the period in which the scarring occurs. Similarly, lung function declined until day 7 and then remained stable. Moreover, alveoli could be reopened until day 3 by ventilation. This was no longer possible from day 7 because alveolar entrances were "sealed" by cells growing over the collapsed

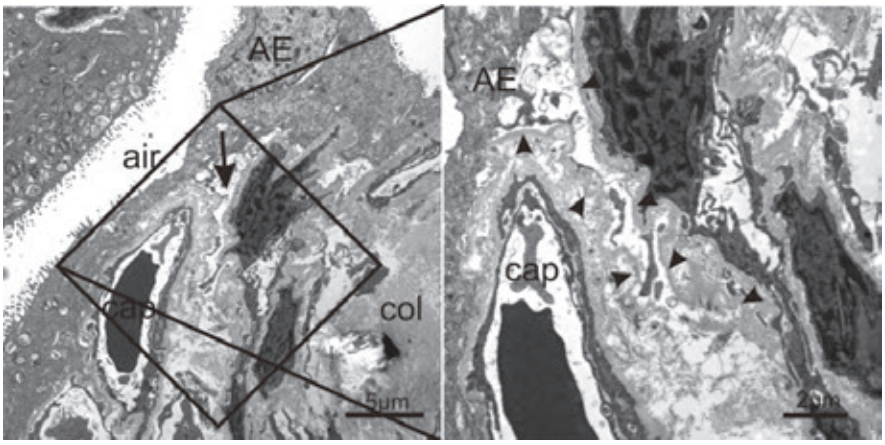



Fig. 2: The phenomenon of collapse induration in patients with ideopathic pulmonary fibrosis (IPF) is characterized by the entrances to the alveoli that are „sealed" with cells. The entrance to a human alveolus (left image, arrow) is overgrown by an alveolar epithelial cell. The basal lamina (right image, arrowheads) usually marks the outline of the alveolar wall. Here it can be traced deeply into the connective tissue (air = airspace; cap = capillary; col = collagen).

entrance. Similar observations were made in samples from IPF patients (Fig. 2). This phenomenon is termed collapse induration. As the data from the animal model show, the decline in lung function starts already with the collapse of alveoli and not just with the scarring, which happens later. Thus, it is necessary not only to address the scarring process therapeutically but also to consider treatment strategies with the goal to stabilize alveoli early.

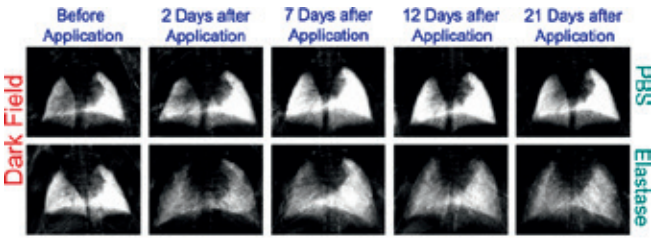
**Further information:**

Lutz D, Gazdhar A, Lopez-Rodriguez E, Ruppert C, Mahavadi P, Günther A, Klepetko W, Bates JH, Smith B, Geiser T, Ochs M, Knudsen L. Alveolar derecruitment and collapse induration as crucial mechanisms in lung injury and fibrosis. American Journal of Respiratory Cell and Molecular Biology. 2015, 52:232-243.

## Research Highlight Radiology 2015

### X-ray absorption and dark-field radiographs of mice in various stages of emphysema severity

X-ray dark-field imaging is a newly developed radiographic imaging method. Because of the strong dark-field signal of lung tissue, X-ray dark-field radiography is of particular interest for the diagnosis of pulmonary disorders. The strong signal is due to scattering of X-rays at each tissue-air interface of the alveolar microstructure. Thus, the dark-field signal yields information about alveolar structures that is not accessible by conventional radiographic imaging. Using a murine emphysema model we were able to show that the diagnosis of pulmonary emphysema is considerably facilitated when using dark-field radiography: Mainly due to a strong increase in sensitivity, even early stages of emphysema were reliably diagnosed. Furthermore, with X-ray dark-field radiography a graduation into different stages of emphysema is feasible. Nothing of this is possible using conventional absorption imaging.




Dark-field imaging yields information about the number and condition of the alveoli in the lung, without having to resolve them directly. In the absorption (top rows) and dark-field X-ray images (bottom row) of healthy mice (left), of mice with a mild (center left), moderate (center right) and severe (right) form of pulmonary emphysema, the loss of signal intensity is clearly recognizable. This is caused by changes in the lung structure due to the disease. Progress of the pulmonary emphysema is difficult to replicate in the corresponding absorption images.

**Further information:**

Hellbach K, Yaroshenko A, Meinel FG, Yildirim AO, Conlon TM, Bech M, Mueller M, Velroyen A, Notohamiprodjo M, Bamberg F, Auweter S, Reiser M, Eickelberg O, Pfeiffer F. In Vivo Dark-Field Radiography for Early Diagnosis and Staging of Pulmonary Emphysema. Investigative Radiology. 2015, 50(7):430-5.

# Clinical Trial Board and Clinical Trials

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

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 into 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 have been distributed and the proposals reviewed and evaluated by the DZL Clinical Trial Board in a competitive process. Final funding decisions are approved by the DZL Executive Board, based on the recommendations of the Clinical Trial Board.

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.

In 2015, for the first time, DZL investigators were able to apply for additional funds for the preparation and completion of applications for clinical studies. These additional funds were provided to encourage investigators to apply for funding for clinical trials not only at DZL, but also at DFG and BMBF. Currently, three applications are being prepared with this financial support.

## „Investigator Initiated Trials", die mit DZL-Mitteln gefördert werden

| Coordinating PIs | Disease Area | DZL Partner Site(s) Involved | Title |
|---|---|---|---|
| Mall | Cystic Fibrosis | All | 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 | Lung Cancer | 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 |
| Behr/Günther | Diffuse Parenchymal Lung Disease | 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 |
| Heußel | Lung Cancer | All | Early response capturing in the treatment of adenocarcinoma |
| Griese | Diffuse Parenchymal Lung Disease | All | Hydroxychloroquine (HCQ) in pediatric ILD (= children´s interstitial lung disease; chILD) |
| Tümmler | Cystic Fibrosis | BREATH, TLRC, UGMLC | Orkambifacts – Intestinal current measurements (ICM) to evaluate the activation of mutant CFTR in treated with lumacaftor in combination with ivacaftor. |
| Vogel-Claussen | Radiology/ Pulmonary Hypertension | BREATH, CPC, UGMLC, TLRC | Change-MRI – Phase III diagnostic trial to demonstrate that functional lung MRI can replace VQ-SPECT in a diagnostic strategy for patients with suspected CTEPH. |

# Technology Transfer Consortium

| | |
|---|---|
| Chairmen | Dr. Christian Stein (Managing Director, Ascenion GmbH) |
| | Dr. Peter Stumpf (Managing Director, TransMIT GmbH) |
| Scientific Advisor | Prof. Dr. Werner Seeger (DZL Chairman) |

Efficient and effective exploitation of research results remains a key priority of the DZL. The DZL Technology Transfer Consortium, founded in 2013, is made up of representatives from the technology transfer organizations of all DZL partners as well as representatives from DZL, among them Prof. Dr. Werner Seeger (Chairman of the DZL), who acts as Scientific Advisor, and Dr. Annegret Zurawski, Manager of BREATH (Hannover).

The Consortium provides key services to DZL members including:

- 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 review meetings with BfArM with the aim of minimizing potential procedural errors

The institutions participating in the DZL Technology Transfer Consortium are:

ascenion

EMBLEM TECHNOLOGY TRANSFER

Max-Planck-Innovation

dkfz. DEUTSCHES KREBSFORSCHUNGSZENTRUM IN DER HELMHOLTZ-GEMEINSCHAFT

technology transfer heidelberg

Fraunhofer

TransMIT Gesellschaft für Technologietransfer mbH

The DZL Technology Transfer Consortium screened all abstracts submitted for the 2015 Annual Meeting and identified several that had potential intellectual property considerations.

# Cooperations, Collaborations and DZL Networks

In the German Center for Lung Research (DZL), more than 200 scientists and their work groups, currently from a total of 24 university and non-university research institutions as well as clinics at five sites in Germany, all work together. Thus there is an intensive exchange, both between DZL researchers amongst the sites and also within the whole network, with external partners of particular importance, all devoting themselves to their common goal, to research and combat lung diseases to the best of their ability. Besides weekly telephone conferences and numerous annual meetings of the work groups, committees and administrative units, two large annual DZL meetings should be highlighted: the Annual Meeting, at which all DZL, including numerous junior researchers all get together to exchange views on the status of their projects, and the International Symposium with high-ranking faculty, promoting scientific exchange with international work groups.

More than 400 scientists and clinicians met on 26 and 27 January, 2015, at the **4th DZL Annual Meeting in Hamburg**. In the assembly, DZL researchers gave presentations on the scientific highlights of all eight Disease Areas being researched at the Center. The Chairman of DZL, Prof. Dr. Werner Seeger and the Scientific Officer of DZL, Dr. Megan Grether (2013-2015) gave updates on the developments across the DZL sites. Visiting members of the International Scientific Advisory Board spoke convincingly of the progress of the Center. Eight of the nine members attended the meeting and met with the DZL Board to discuss new strategies for the coming funding period. A new addition to the program of the Disease Areas was the Best Abstract Competition that preceded the meeting. One young researcher per Disease Area was selected by the Organizing Committee to give a short presentation of his/her poster abstract before the assembly. Participants also had discussions at over 200 posters. On the second day, the work groups from the Disease Areas and Platforms met to discuss current projects and the research program for the next funding period. At the Annual Meeting, the eleven mentees from the first year of the DZL Mentoring Program „Careers in

4th DZL Annual Meeting in Hamburg

Respiratory Medicine" met with their supervising mentors at a kick-off meeting.

Lung experts from all over the world met from 25 to 27 June, 2015 in Heidelberg at the **4th International Symposium of the German Center for Lung Research**. Under the motto „Frontiers in Chronic and Malignant Airways Disease", the conference addressed chronic and malignant airway diseases like cystic fibrosis, COPD (chronic obstructive pulmonary disease) and lung cancer. The symposium focused on the latest research findings concerning pathogenic mechanisms and innovative disease-related approaches to combat pulmonary diseases. In the four plenary sessions: Cystic Fibrosis meets COPD, Mucus and the Microbiome, Molecular and Cell Biology of Lung Diseases and Lung Cancer, leading international experts presented the latest findings from the areas of basic research, translational research and clinical use. Alongside renowned lung experts, young researchers were also given the opportunity to introduce selected contributions in short presentations and also present their projects in three poster sessions. Three poster prizes were awarded by the DZL. The symposium was hosted by the DZL site Translational Lung Research Center in Heidelberg (TLRC).

Moreover, there were numerous other events with involvement of the DZL at the partner sites.

The German Center for Lung Research has, since its founding, been part of several networks to research into various pulmonary diseases and is associated with other organizations that contribute to the realization of research projects. The expansion and development of the **partnerships in the fields of science and research, youth development, patient information and interests, clinical studies, industry and educational work** continue to be actively pursued. Numerous **cooperations on a national and international basis**


4th International Symposium of the German Center for Lung Research

strengthen the position of the DZL as an outstanding institution and the largest German research network in the field of pulmonary research.

The DZL cooperates closely with the **Lung Information Service (LIS)** based at the Helmholtz Center in Munich and supports the range of easy-to-understand information from research and clinic all about pulmonary diseases. The scientists and doctors at the DZL sites take on an advisory role for the editorial contributions of the LIS and individual patient enquiries sent to the LIS. In addition to its online platform, the Lung Information Service also organizes events like patient fora on special themes. Together with the DZL, in 2015 the Lung Information Service also organized patient fora at a number of DZL sites.

The DZL also plans to expand its cooperation with **patient organizations**, to increase awareness of the interests of pulmonary patients.

Ever since the foundation of the DZL, there has been a close cooperation with **COSYCONET (German COPD and SYstemic consequences – COmorbidities NETwork)** through scientists belonging to both institutions. Thirty-one study centers are involved in the German-wide register for the pulmonary disease COPD, that is the fourth highest cause of death worldwide. As part of the cohort study COSYCONET, a long-term observation of more than 2,700 COPD patients will be carried out. The investigations should provide new data on the development of the disease, its level of severity and its comorbidities. COSYCONET has at its disposal a biobank, an image bank and phenotypic data, that serves as a basis for various subprojects. At the start of 2016, COSYCONET will be integrated into the DZL as an associate partner.

Since the start of 2013, **CAPNETZ (German Competence Network for Community-Acquired Pneumonia)** has been an associate partner of the DZL. The Competence Network has set itself a goal of acquiring new knowledge about the origin and course of Community-Acquired Pneumonia (CAP), developing improved diagnostic standards and therapies, and strengthening methods of clarification and prevention. Community-acquired pneumonia is still a potentially life-threatening disease and is the sixth highest cause of death in Germany. With the largest Europe-wide comprehensive epidemiological study, with over 10,000 CAP patients, and the most extensive CAP database in the world, the DZL has gained a strong partner. The DZL has thus also expanded its network even further, increasing its number of scientists and study centers in Europe. For instance, CAPNETZ is involved in PREPARE (Platform foR European Preparedness Against (Re-)emerging Epidemics), one of the programs funded by the European Union to carry out research into infections with epidemic potential.

**Registries and patient cohorts** are of great and increasing importance for translational research. Large cohorts and registries will be brought into the DZL by associated institutions. For example, together with CAPNETZ, the DZL has been involved since 2015 in the establishment of the bronchiectasis registry **PROGNOSIS (The Prospective German Non-CF-Bronchiectasis Registry)** and the pediatric CAP cohort **Ped-CAPNETZ**. PROGNOSIS is, in addition, part of the EU-funded European registry **EMBARC (European Multicentre Bronchiectasis Audit and Research Collaboration)**. DZL scientists are also actively involved in many other registries and cohorts, e.g. in the pulmonary hypertension registry **COMPERA (Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension)** or in the **National Cohort (NAKO)**.

The **National Cohort**, started in 2014, is to date the largest German population study researching widespread diseases (epidemics). The DZL is already connected with the National Cohort through scientists from its own ranks and has entered into negotiations to establish a contractually fixed cooperation. Thus, amongst other things, a project on the prevalence of pulmonary health and disease as well as other cooperations are envisaged.

The German Center for Lung Research, through its researchers and sites, also works together with **PROGRESS (Pneumonia Research Network on Genetic Resistance and Susceptibility for the Evolution of Severe Sepsis)**. Research is being carried out on the genetic basis for disease pathogene-

sis and the resistance to community-acquired pneumonia. The main focus of the research is the question of which factors influence whether pneumonia will take an uncomplicated or a difficult course – even up to a septic shock. PROGRESS will become an associate partner in the DZL in 2017.

At the end of 2015, the Board of DZL decided to admit the **Pulmonary Research Institute (PRI)**, based at the LungenClinic Grosshansdorf and already working closely together with the Center, as an associated partner. The PRI has at its disposal an extensive range of methods for the investigation of functional alterations and inflammatory processes of the lung. Cohort projects in the field of COPD and bronchial asthma will be carried out as well as Phase I-IV clinical studies in the field of respiratory medicine, focusing on COPD, bronchial asthma and other more rare disorders. The already longstanding close cooperation with the LungenClinic Grosshansdorf and the DZL will now be intensified through this new partnership.

Since the start of the DZL, the **German Respiratory Society (Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin e. V., DGP)** has been an important strategic partner of the Center. Cooperations, e.g. in the field of sponsoring young pulmonary scientists and doctors as well as in the field of exchanges with patient organizations will continue to be strengthened. In addition, the DZL regularly publishes its „Mitteilungsseiten" (announcement pages) in the DGP official journal, „Pneumologie". At the Annual Meeting of the DGP, the German Center for Lung Research is regularly represented with an information stand and presentations. Members of the DZL Board and DZL scientists have held and continue to hold significant positions within the DGP and thus play some part in supporting joint activities.

The **German Society for Pediatric Pneumology e. V. (GPP)** promotes research, networking and the exchange of scientists and clinicians as well as the dissemination of new findings in the field of pediatric respiratory medicine. Thus, the GPP is an important partner in the field of pediatric pneumology. The GPP regularly organizes scientific symposia and workshops, integrating the research content of the DZL. DZL researchers also hold key positions within the GPP and are very much involved in the scientific work groups of the society. In this way, the scientific exchange between the GPP and the DZL is promoted.

Since 2013, the DZL is a full member of the **Technology, Methods and Infrastructure for Networked Medical Research e. V. (TMF)**, the parent organization for joint medical research in Germany. Particularly in the field of biobanking and when establishing a central data management, the DZL cooperates closely with the TMF. Especially in the field of biobanking, regular and intensive exchange with the biobank and IT representatives from the German health research centers and the German Biobank Node (GBN) takes place.

The **Robert Koch Institute (RKI)** is the central facility of the German government in the field of applied and action-oriented biomedical research. It has a unique population-based database for non-communicable as well as communicable pulmonary diseases. An associate partnership with the RKI is in preparation since 2015. The expertise of the DZL can thus be greatly strengthened in the important field of epidemiology. Use of RKI-relevant data will, in particular, contribute to DZL research in the Disease Areas of Asthma and Allergy, COPD, Pneumonia and Acute Lung Injury as well as Lung Cancer. In addition, a cooperation is envisaged in various pilot projects on infections.

The DZL also supports various anti-smoking campaigns. One of these is the initiative **Education against Tabacco (Aufklärung gegen Tabak e. V., AGT)**, that focuses on juveniles. Medical students from 30 faculties in Germany, Austria and Switzerland inform approximately 20,000 pupils from the 6th to 8th classes each year about the dangers of smoking tobacco and campaign for smoke-free classes. Together with the students, teachers, doctors and professors are all involved in the project. The DZL Chairman and further DZL researchers are members of the initiative's Scientific Advisory Board.

Together with the other **German Centers for Health Research (Deutsche Zentren der Gesundheitsforschung - DZG)**, the DZL is part of a German-wide network in medical research. The DZG profits from the regular exchange of information on joint strategic, infrastructural and scientific

subjects on many different work levels. For the benefit of the patients, in this way synergistic effects can be created where, for instance, topics in pulmonary, cancer, infection or cardiovascular research can overlap, as in the case of lung cancer, COPD, pneumonia or pulmonary hypertension. A joint objective of the DZG is the continuous access to information from decision-makers and the broader public, as is the case at the annual World Health Summit or other congresses and events.

In cooperation with the French National Institute of Health and Medical Research, **Inserm (Institut national de la santé et de la recherche médicale)** and sponsorship from the BMBF on the German side, the DZL offers young researchers the possibility of direct bilateral exchange. One German and one French partner in each case work together on a project that includes alternating stays in the respective research institutes in the other country. For doctoral and post-doctoral students, both countries also comprehensive workshops, symposia and summer or winter schools.

The **European Respiratory Society (ERS)**, one of the largest and most significant societies in the field of respiratory medicine, is an important partner of the DZL. This close association is marked, for example, by charing the annual meeting of the ERS in Munich in 2014 as well as honoring several DZL scientists with the award of Fellow of ERS (FERS). The DZL is regularly represented at the Annual Congress of the European Respiratory Society (ERS) with an information stand and presentations by DZL scientists – as was also the case in 2015 in Amsterdam. The ERS Congress is the largest meeting of respiratory researchers and clinicians in the world.

The individual DZL sites also each enjoy further numerous strategic partnerships with **international scientific and economic partners**.

DZL scientists are currently involved in well over 250 **clinical studies**. Of these, particularly registration-oriented clinical studies with **partners from industry** are conducted and supported. Sponsors of such studies include AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly and Company, GlaxoSmithKline, Hoffmann-La Roche and Novartis/Novartis Pharmaceuticals.

# 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.

## 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 the Universities of Kiel and Lübeck
- Graduate programs from DFG Excellence Initiative
- Borstel Biomedical Research School (BBRS)

*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 (MMRS)
- Helmholtz Graduate School Environmental Health (HELENA)
- Life Science Campus Network Munich

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

*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)

## DZL Mentoring Program

The DZL mentoring program "Careers in Respiratory Medicine" was initiated in 2014 and it kicked off officially in early 2015 at the DZL Annual Meeting in Hamburg. The mentoring program focuses on supporting highly motivated junior DZL scientists working in biomedical science and medicine to plan their careers in order to qualify for leading positions. For each of the meanwhile 20 mentees, there is an individually chosen mentor. The program is complemented by workshops and soft skill courses, e.g. in project and scientific management, communication and conflict management, leadership skills and social competence. At the 2016 DZL Annual Meeting in Hannover, for example, the mentees had the opportunity to participate in a workshop on conversation techniques. They then met with their mentors at a network event to exchange views on their career development and specific research projects. Alongside the existing DZL mentors, a number of other DZL scientists were gained as mentors to strengthen the program in the coming years. A new round of applications is planned for the end of 2016.

## German-French Lung School

The German-French Lung School was launched in 2013 and is coordinated by the DZL site in Munich (CPC-M). Through the creation of this program, German and French students and postdocs engaged in lung research have the opportunity to learn new techniques, exchange views with other scientists 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 at DZL partner sites. In the context of the gender equality programs of the participating university partners, at the DZL priority is placed on the active recruitment of female scientists at every level – from trainees to advisory board members. Particular focus has been placed on increasing the number of female personnel in the DZL, especially in leading positions. Since the founding of the DZL in 2011, the percentage of female Principal Investigators (PIs) has increased from 14% to 21% in 2015, when the percentage of female personnel funded by the DZL had reached 60%.

# The Public Face of the DZL

Despite increasing morbidity rates, there still tends to be insufficient awareness of pulmonary diseases compared to other widespread diseases. It is therefore important to inform the general public, decision-makers, patients and other target groups about pulmonary diseases. The DZL is very involved in the field of public relations, with its own scientific symposia, its presence at national and international congresses, printed information like brochures, flyers and annual reports, patient forums and its internet presence (www.dzl.de), through a Newsletter and cooperation with the Lungeninformationsdienst (German Lung Information Service, www.lugeninformationsdienst.de). The research association also introduces itself in a short film portrait that can be found on the homepage as well as on YouTube. In addition, together with the other German Centers for Health Research (DZG), the DZL organizes events to make various target groups aware of its cause and its activities.


DZL representatives with ERS president Prof. Dr. Elisabeth Bel (2014-2015, second from left)

## DZL at Conventions

In 2015, the DZL was again represented at two large conventions. With an information stand, numerous award winners and presentations by its own scientists, the DZL played a highly visible role at the 56th Congress of the German Respiratory Society (Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin e.V., DGP). The DGP Congress, held in Berlin under the motto "Working together for the patient", represents the largest scientific forum in the field of respiratory medicine in the German-speaking world. Already at the opening event, the German Federal Minister of Health, Hermann Gröhe, acknowledged the DZL and its activities in his welcoming speech. He also emphasized that the importance of respiratory medicine must be brought more to the attention of the general population and public awareness of it increased. In this, the German Lung Information Service, cooperating closely with the DZL, also provides with its activities a valuable bridge between patients, relatives and science.

In September 2015, the German Center for Lung Research was well represented at the ERS (European Respiratory Society) International Congress in Amsterdam, e.g. with award winners, presenters and presentation chairs. In addition, together with other professional associations from around the world in the congress area World Village, the DZL had its own stand, providing information on its activities and receiving the ERS President, Prof. Dr. Elisabeth Bel, during the annual President's Visit. More than 22,000 people from more than 120 countries participated in the largest congress on respiratory medicine in the world. A presence at congresses, like those of the DGP or the ERS, also contributes towards making the DZL more visible, both nationally and internationally.

## DZL Events for the Scientific Community

Internal communication is, in a large research association like the DZL, that unites scientists from numerous partner institutes from different sites in Germany, of particularly great importance. Here, personal exchange of views is essential, even in today's world of modern media. The most important and largest meeting is the DZL Annual Meeting, that takes place at all the Center's sites on a rotating basis. In January 2015, more than 400 scientists, clinicians and young researchers discussed project results and goals at the 4th DZL Annual Meeting in Hamburg. The work groups of the Disease Areas and platforms take advantage of the opportunity for mutual exchange of views and strategic consultation.

In order to be able to research and treat pulmonary diseases more effectively, it is essential to also communicate intensive-

ly beyond national borders. The International DZL Symposium, held annually, contributes to this. The 4th International DZL Symposium in June 2015 in Heidelberg brought together roughly 200 highly acclaimed lung researchers from throughout the world. Under the motto "Frontiers in Chronic and Malignant Airways Disease", the conference addressed chronic and malignant airway diseases like cystic fibrosis, COPD (chronic obstructive pulmonary disease) and lung cancer. A focus of the symposium were the latest research findings on pathogenic mechanisms and innovative disease-spanning processes in the fight against pulmonary disease.

In addition, in 2015 numerous further local scientific events took place with DZL participation at the sites of the research association.

## Working together for Health Research – DZG Events

At the beginning of February 2015, the six German Centers for Health Research (DZG) held a "Parliamentary Evening" in Berlin. After a podium discussion, the Centers used the opportunity to present to the political representatives and policymakers their plans for the rapid translation of research knowledge into clinical practice. At the DZL round table discussion, those present then had the possibility to learn more about the Association and its translational projects.

Parliamentary Evening of the DZG in Berlin

In October 2015, the DZL, together with the other German Centers for Health Research (DZG), also organized a round table discussion on translational research at the World Health Summit in Berlin. In 2015, the subject of promotion of young scientists, under the motto "Education and Training of Clinical and Translational Scientists – Different Models in Different Countries" was the main focus of the DZG Forum.

## The DZL on TV and Radio, in Print and Online

In 2015, the DZL homepage was also launched in German. The special homepage category "New this week in PubMed" gives a weekly overview of the latest publications by DZL scientists. During the year, diverse papers by DZL researchers were published in specialist journals and in the press. In December, a special section on the lung was published in the Frankfurter Allgemeine Zeitung (FAZ) with numerous expert contributions by DZL scientists, interviews with the DZL researchers and further background information. The comprehensive DZL Annual Report 2014 was published in 2015 both in English and in German. Together with achievements and highlights from the year 2014, the report presented the numerous successes of the DZL since its foundation. New editions of the regularly published "DZL-Mitteilungsseiten" in the specialist journal "Pneumologie" continued in 2015. A media highlight was the televising by the ZDF (Second German Television) of the presentation of the 2015 German President's Award for Innovation in Science and Technology to the DZL Project Leader, Prof. Dr. Ardeschir Ghofrani and his team in December. Dr. Ghofrani and his team, working together with the Bayer pharmaceutical company, have developed a new drug for the treatment of two life-threatening forms of pulmonary hypertension and successfully brought it to international registration. The German Federal President, Joachim Gauck, presented the 250,000 Euro award in Berlin.

## Focusing on Patients

During the year, the DZL organized four different forums for patients and their relatives, three of them together with the German Lung Information Service (LIS). In February, the Patient Forum on Cystic Fibrosis took place in Heidelberg and in March, the BREATH site in Hannover held the 10th Lung Forum on Bronchiectasis. In April, the Patient Forum on the Lung series achieved a record number of 150 participants at a patient seminar on "COPD – Living with a chronic disease" at the DZL site ARCN at the LungenClinic Grosshansdorf near Hamburg. The 12th Lung Forum under the motto "When breathing becomes difficult - Asthma in childhood and as an adult" was organized by the German Lung Information Service together with the DZL site CPC-M (Munich) in October 2015.

Record number of 150 participants at the 11th patient seminar at the LungenClinic Grosshansdorf near Hamburg

## 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 (www.lungeninformationsdienst.de) containing comprehensive, up-to-date, accurate and unbiased information on lung diseases that is accessible to the general public and easily understandable.

**Special Topics Addressed by the Lung Information Service on their Website in 2015:**

- Viral Infections (January)
- Immunotherapy (February)
- Bronchoscopy (March)
- Protection against Radon (April)
- Complications after Lung Transplantation (May)
- Pulmonary Hypertension (June)
- COPD and Pulmonary Emphysema (July)
- Epigenetics (August)
- Diagnostic Imaging (September
- Regeneration and Remodeling (October)
- Cystic Fibrosis (November)
- Tuberculosis (December)

An important source of LIS information are articles published on patient-relevant topics in top scientific journals, including an increasing proportion with DZL authorship. In addition, the LIS regularly publishes expert interviews on current issues in lung research, including video interviews with leading DZL scientists, e.g. in 2015 with Prof. Erika von Mutius and Prof. Dr. Dennis Nowak. The LIS also publishes on special topics each month, as well as on current questions with regard to disease areas, diagnostic methods and therapies. In addition to purely scientific content, it publishes information about patient-relevant events, literature recommendations for patients, and announcements of interesting lung-relevant television and radio broadcasts.

From 2011-2015, the LIS published more than 500 news articles on its website. Furthermore, the LIS offers a monthly newsletter and also has its own Facebook page. In late 2011, a very popular series of patient information forums covering a breadth of topics from various lung diseases was started. In 2015, LIS and DZL sites held several patient forums in Hannover (topic: bronchiectasis), Großhansdorf (topic: COPD) and Munich (topic: asthma). The LIS was also represented in 2015 with information stands at further events, like the Lung Symposium in Hattingen, and held a Round Table Meeting with representatives of patient organizations, to receive feedback and suggestions for topics to cover.

# Highlights of the Year 2015

## January

Over 400 participants attended the **4th Annual Meeting of the German Center for Lung Research** in Hamburg on 26 and 27 January 2015, during which the **DZL Mentoring-Program** was launched.

## February

On 2 February 2015, the DZL co-organized the **Parliamentary Evening of the German Centers for Health Research** in Berlin. DZL scientists explained to the visitors concrete examples of translational pulmonary research, amongst them the development process for Riociguat, the drug for use in pulmonary hypertension.

## March


The German Federal Minister of Health, Bundesgesundheitsminister Hermann Gröhe acknowledged the DZL in his welcoming speech at the **56th DGP Congress** as a successful merger of translational lung research in Germany and for its further promotion of young scientists. The DZL was represented at the Congress with numerous award winners, scientific contributions and an information stand.

## April

**A record number of over 150 visitors** was achieved by the **Patient Forum on the Lung** series at its 11th event on "COPD – Living with a chronic disease" at the DZL site ARCN at the LungenClinic Grosshansdorf.

## May

The **new substance SB010 for treatment of allergic asthma was successfully tested by DZL scientists at the Hannover and Marburg sites**. The researchers reported on this in a joint publication in the renowned New England Journal of Medicine.

## June

Lung experts from throughout the world met from 25 to 27 June 2015 in Heidelberg at the **4th International Symposium of the German Center for Lung Research** under the motto "Frontiers in Chronic and Malignant Airways Disease".

## July

**A novel therapeutic option for the treatment of a type of non-small cell lung cancer was developed together with a DZL scientist and successfully tested.** The work was published in the renowned journal The New England Journal of Medicine.

## August

The German Center for Lung Research submitted its **Report on the evaluation of the 1st period of funding**. The international board of reviewers subsequently awarded the DZL the highest marks for its "enormous progress" and "substantial success" in the fight against widespread respiratory diseases.

## September

The DZL again attended the **International Congress of the European Respiratory Society** from 26 to 30 September 2015 in Amsterdam and was represented by numerous speakers, award winners and an information stand at the world's largest lung conference.

## October

The DZL participated in the **joint forum of the German Centers for Health Research (DZG) at the World Health Summit** on 13 October 2015 in Berlin on the topic of education and training of clinical and translational scientists.

## November

At the **7th Discussion Forum of the German Centers for Health Research** on 6 November 2015, the speakers and management of the DZG as well representatives from the BMBF met to exchange views on strategic, infrastructural and economic topics.

## December

The DZL researcher, Prof. Dr. Ardeschir Ghofrani and his colleagues from Bayer were awarded the **2015 German President's Award for Innovation in Science and Technology** by the German Federal President, Joachim Gauck, **for the development of the drug "Riociguat" for the treatment of pulmonary hypertension.**

# Selected Prizes and Awards 2015

| Award winner | Award |
|---|---|
| **Prof. Dr. Roland Diel**<br>Großhansdorf | Elected "Fellow of ERS" (FERS)* |
| **Prof Dr. H. Ardeschir Ghofrani**<br>Giessen /Bad Nauheim | German President's Award for Innovation in Science and Technology |
| **Dr. Christine Happle** und **Dr. Nico Lachmann**<br>Hannover (Junior Researchers) | DGP** Research prize for outstanding work in the field of clinical research |
| **Prof. Dr. Rudolf M. Huber**<br>Munich | Global Governor and Nominating Committee CHEST |
| **PD Dr. Sebastian Kobold**<br>Munich | Habilitation prize from the Ludwig Maximilian University of Munich |
| **Prof. Dr. Michael Kreuter**<br>Heidelberg | Research Award of the Patienten-Selbsthilfeorganisation Lungenfibrose e. V. (patient self-help organization for pulmonary fibrosis) for outstanding work in the field of clinical research |
| **Dr. Lavinia Mägel**<br>Hannover (Junior Researcher) | Price of the Deutschen Lungenstiftung e. V. (German Lung Foundation) for the best experimental doctoral thesis in the field of pneumology |
| **Prof. Dr. Ulrich A. Maus**<br>Hannover | Research Award of the Patienten-Selbsthilfeorganisation Lungenfibrose e. V. (patient self-help organization for pulmonary fibrosis) |
| **Prof. Dr. Erika von Mutius**<br>Munich | Elected "Fellow of ERS" Annual Margaret Turner Warwick Respiratory Lecture 2015 |
| **Prof. Dr. Antje Prasse**<br>Hannover | ERS Research Award on Idiopathic Pulmonary Fibrosis |
| **Dr. Rajkumar Savai**<br>Giessen / Bad Nauheim | ERS Sir John Vane Grant for Best Recent Publication in Pulmonary Vascular Research |
| Dr. Soni Savai Pullamsetti Bad Nauheim / Giessen | DGP Research Award for outstanding work in the field of basic research |

*(in alphabetical order: *ERS = European Respiratory Society (The ERS awards "Fellow of ERS (FERS)" to excellent lung researchers and clinicians), **DGP = Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin e. V.)*

# The German Centers for Health Research

DZG DEUTSCHE ZENTREN DER GESUNDHEITSFORSCHUNG

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 to achieve this goal, the German Federal Ministry of Education and Research (BMBF) 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 gaps in knowledge and to improving prevention, diagnosis and treatment of diseases. The aim is to achieve the highest possible level of therapeutic efficacy for each patient. The Centers' research policy emphasizes the close cooperation between the basic and clinical research of all partners, based on the indications and the needs of the patients. This close networking and expansion of existing research structures allow faster transfer of research findings into clinical practice (translational research).

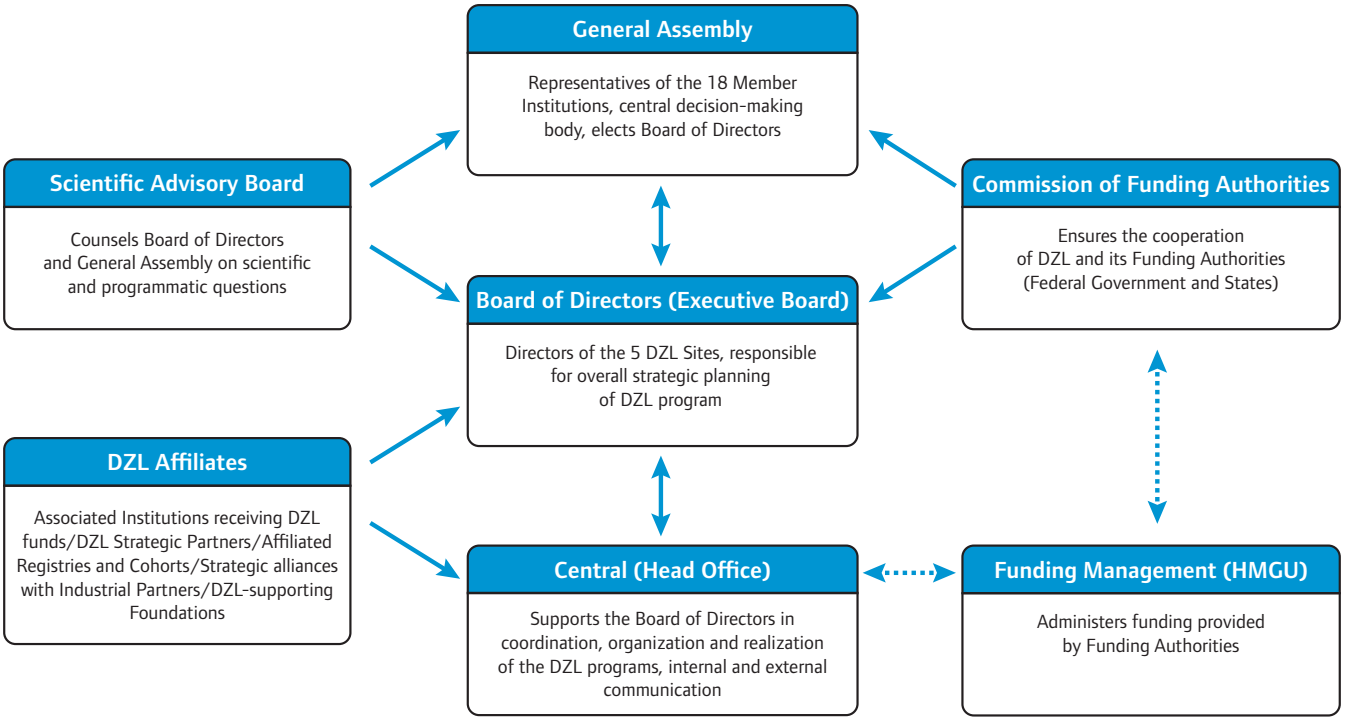
In the long term, the strategic collaboration of leading scientists in the German Centers for Health Research will make Germany internationally more competitive on the research level and markedly more attractive for young researchers both within Germany and from around the world.

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 coordinates the joint research activities of all partners at their respective center as well as the division of tasks and use of resources for all sites, in accordance with the jointly defined research priorities

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

Speakers and representatives of the six German Centers for Health Research present achievements of their translational research at the joint Parliamentary Evening in Berlin

# DZL Organization




| ARCN | BREATH | CPC-M | TLRC | UGMLC |
|---|---|---|---|---|
| 4 Member Intitutions + 3 Associated Partners | 3 Member Intitutions + 1 Associated Partners | 3 Member Intitutions + 1 Associated Partner | 5 Member Intitutions | 3 Member Intitutions + 1 Associated Partners |

## DZL Executive Board

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

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## Scientific Advisory Board

**Jacob I. Sznajder, MD**
(Chairman of the Advisory Board) – Chief, Division of Medicine-Pulmonary, Ernest S. Bazley Professor of Asthma and Related Disorders, Northwestern University Feinberg School of Medicine, Chicago

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

**Rachel Chambers, PhD**
Professor of Respiratory Cell and Molecular Biology, Centre for Inflammation and Tissue Repair, UCL Respiratory, University College London

**Jeffrey M. Drazen, MD**
Distinguished Parker B. Francis Professor of Medicine, Harvard Medical School; Editor-in-Chief, The 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)

**Peter M. Suter, MD**
Akademien der Wissenschaften Schweiz, Centre Médical Universitaire, Université de Genève

## Heads of Funding Management Office

- Dr. Dorothe Burggraf – Finance Department (Commercial Funding Management)
- Dr. Stefan Echinger – Department of Operations & Support (Scientific Funding Management, until March 2016)

## General Assembly

Currently, 18 member institutions belong to the DZL. In addition, the DZL has six Associated Partners (as at 2016)

## Commission of Funding Authorities

- German Federal Ministry of Education and Research (Bundesministerium für Bildung und Forschung): Chair
- Baden-Württemberg – Ministry of Science, Research and the Arts Baden-Württemberg
- Bavaria – Bavarian State Ministry of Education and Cultural Affairs, Science and the Arts
- Hessen – Hessian Ministry for Science and the Arts
- Lower Saxony – Lower Saxony Ministry of Science and Cultural Affairs
- Schleswig-Holstein – Ministry of Social Affairs, Health, Science and Equality

# DZL Cooperating Partners


**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

Pneumologisches Forschungsinstitut (PRI) an der 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

German COPD and Systemic Consequences – Comorbidities Network (COSYCONET)

**DIRECTOR**

Prof. Dr. Werner Seeger

Speaker and Chairman of the DZL

**MÜNCHEN**

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 Borstel, Lübeck, Kiel, Großhansdorf
## Airway Research Center North (ARCN)

### Partner Institutions of the DZL Site

- Research Center Borstel – Leibniz-Center for Medicine and Biosciences
- University of Lübeck
- University Medical Center Schleswig-Holstein, Lübeck Campus
- University Medical Center Schleswig-Holstein, Kiel Campus
- Christian-Albrechts-University Kiel
- LungenClinic Grosshansdorf
- Pulmonary Research Institute at the Lung Clinic Grosshansdorf

### Prof. Dr. Klaus F. Rabe

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### Research Profile

Scientists and clinicians of the Airway Research Center North (ARCN) focus on research on chronic obstructive pulmonary disease (COPD) and 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. As the biggest North German clinic specializing in lung and airway diseases with more than 13,000 patients treated per year, the LungenClinic Grosshansdorf is, together with the University Clinic Schleswig-Holstein (UKSH) and the Medical Clinic Borstel, responsible for clinical and patient-oriented research in the ARCN. The Research Center Borstel focuses on the investigation of infectious as well as non-infectious lung diseases and contributes to the success of ARCN basic research and the development of 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. Cohort projects and clinical studies are conducted together with the Pulmonary Research Insitute at the LungClinic Grosshansdorf. To strengthen the connection between clinical and basic research, the Biomaterialbank Nord has been set up as a joint central infrastructure. This crosslink between complementary partners in the ARCN is intended to support the collaborative implementation of translational research strategies.

# DZL Site Hannover

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

### Partner Institutions of the DZL Site

- Hannover Medical School (MHH)
- The Fraunhofer Institute for Toxicology and Experimental Medicine (ITEM), Hannover
- Leibniz University Hannover (LUH)
- CAPNETZ Foundation

### 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 Foundation
- Head of the Competence Center for Infectious Diseases
- Director of the Competence Network AsCoNet
- President of the German Respiratory Society (DGP), 2013–2015
- Fellow of ERS (FERS), elected in 2014

### Contact

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### Research Profile

The focus of BREATH is the translation of findings from basic research into clinical practice, with regard to all topics listed below, including the execution of clinical studies of all phases. With the opening of the Clinical Research Center Hannover in 2015, a joint initiative of the federal government and the State of Lower Saxony, the last gap in this area was closed successfully. Hannover Medical School is one of the three largest Lung Transplantation Centers in the world, and research in end-stage lung diseases is therefore one of the core areas of BREATH. Other closely connected aspects are research on an artificial lung and stem cell research. Pre-clinical research is extensively performed in the areas of infection, pulmonary hypertension, interstitial lung diseases as well as asthma and allergies. In the area of basic research, BREATH focuses on the pathobiology of bacterial infections of the lung. In cooperation with the Fraunhofer Institute for Toxicology and Experimental Medicine, research is conducted on the pathophysiology of allergic diseases. The Leibniz University adds expertise in health services research and health economic aspects as well as in the area of imaging based on laser techniques. The national research network CAPNETZ aims to improve the patient-centered care for adults and children with community-acquired pneumonia (CAP), and is also involved in the construction of the bronchiectasis registry PROGNOSIS.

# DZL Site Munich
## Comprehensive Pneumology Center Munich (CPC-M)

### Partner Institutions of the DZL Site

- Helmholtz Zentrum München – German Research 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

### Contact

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### 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 have come together to form one of the largest centers for translational research on chronic lung disease in the world. The Helmholtz Zentrum München is a renowned expert in linking 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". The German-French Lung School together with the CPC Graduate Program "Lung Biology and Disease" are coordinated from Munich. 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.

# DZL Site Heidelberg
## Translational Lung Research Center Heidelberg (TLRC)

### Partner Institutions of the DZL Site

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

### Prof. Dr. Marcus A. Mall

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

### Contact

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### Research Profile

The Heidelberg Translational Lung Research Center (TLRC) is an interdisciplinary center for translational lung research in which physicians and scientists at Heidelberg University Hospital and the Medical Faculty of Heidelberg University, the Thorax Clinic at the University Hospital (one of Germany's oldest and largest hospitals specializing in lung diseases), and the non-university research centers - the German Center for Cancer Research, and the European Molecular Biology Laboratory – all work together to combat lung disease. The 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 research. 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. TLRC scientists also contribute to research on asthma and allergy, pneumonia and acute lung injury, pulmonary hypertension and lung fibrosis. 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. Use is made 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. At the TLRC, systems biology is applied to improve our understanding of the molecular causes of lung cancer. The biobank and imaging platforms are central to the success of the translational lung research program. Early clinical trials are conducted to make new diagnostic and therapeutic strategies available to patients in a timely manner.

# DZL Site Giessen, Marburg, Bad Nauheim

## Universities of Giessen and Marburg Lung Center (UGMLC)

### Partner Institutions of the DZL Site

- Justus Liebig University Giessen
- Philipps University Marburg
- Max Planck Institute for Heart and Lung Research Bad Nauheim
- German COPD and Systemic Consequences – Comorbidities Network (COSYCONET)

### Prof. Dr. Werner Seeger

- Chairman and Speaker of the German Center for Lung Research (DZL, National Center)
- Director of UGMLC
- Director of Medical Clinic and Polyclinic II/Head of the Department of Internal Medicine, Justus Liebig University Giessen
- Director, Department of Lung Development and Remodeling, Max Planck Institute for Heart and Lung Research, Bad Nauheim
- Speaker of the Excellence Cluster "Cardio-Pulmonary System" (ECCPS)
- Fellow of ERS (FERS), elected in 2014

### Contact

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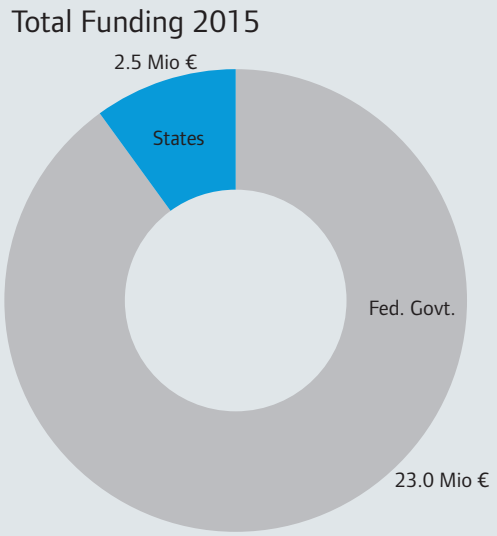
### Research Profile

Translational research at the Universities of Giessen and Marburg Lung Center (UGMLC) focuses on lung diseases caused by inflammatory and hyperproliferative processes. This includes research on the antenatal and postnatal 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 to develop efficient regenerative therapies are studied in the Disease Areas Lung Fibrosis (DPLD) and Pulmonary Hypertension (PH). The UGMLC partners complement one another through a close interplay of basic research and clinical research, based on the cooperation of the Max Planck Institute, the universities and the university hospital. Marburg focuses on the areas of asthma and COPD, Giessen on DPLD and PH, whereby Giessen can be regarded as a national and international center for these diseases. The Max Planck Institute in Bad Nauheim focuses on 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 Head Office as well as the DZL Biobank and Data Management Platform.

# Finances and Personnel

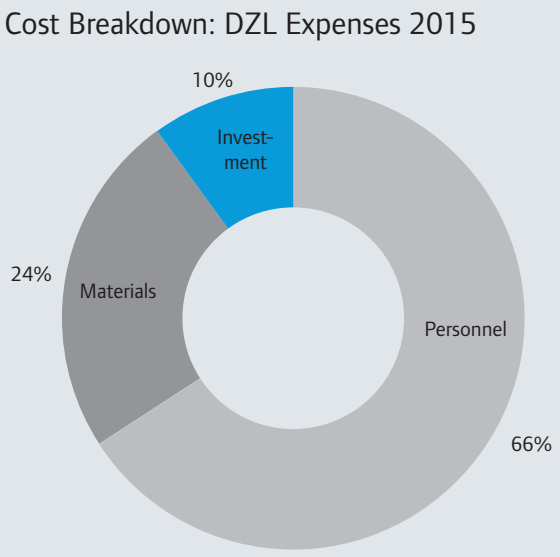


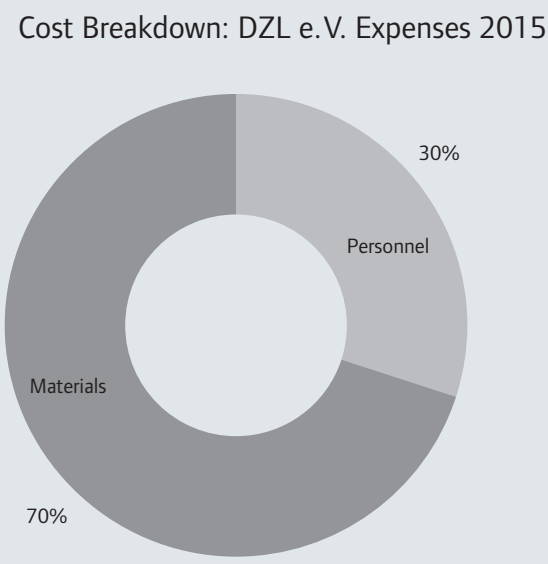

## Total Funding 2015 (as at July 2016)

The total funding for the DZL in 2015 was € 25.5 Million. 90% was received from the Federal government (BMBF) and 10% from the five German states with participating DZL Centers. Across the eight disease areas studied by DZL scientists, more than 50 major research projects are addressed.

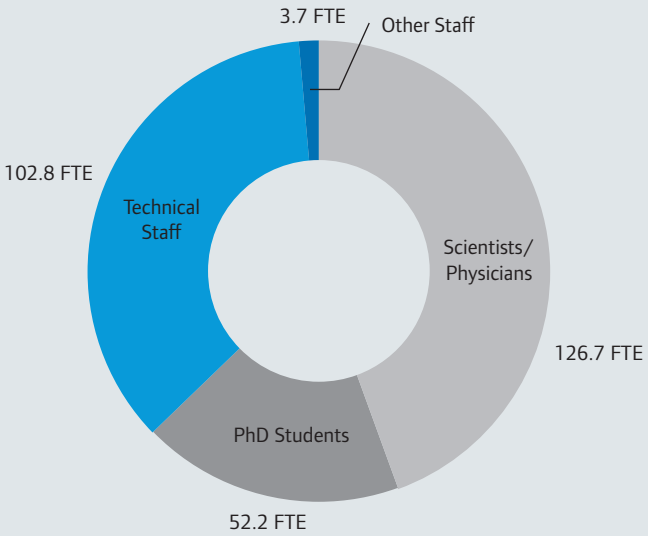
## Cost Breakdown – DZL Expenses 2015 (as at July 2016)

The DZL e. V. is financed through membership fees collected from each member institution. As in previous year, this amounts to € 325,000 in 2015. The 2015 Annual Financial Statement and Year-end Close of the DZL e. V. was conducted by the firm Haas & Haas (Giessen).



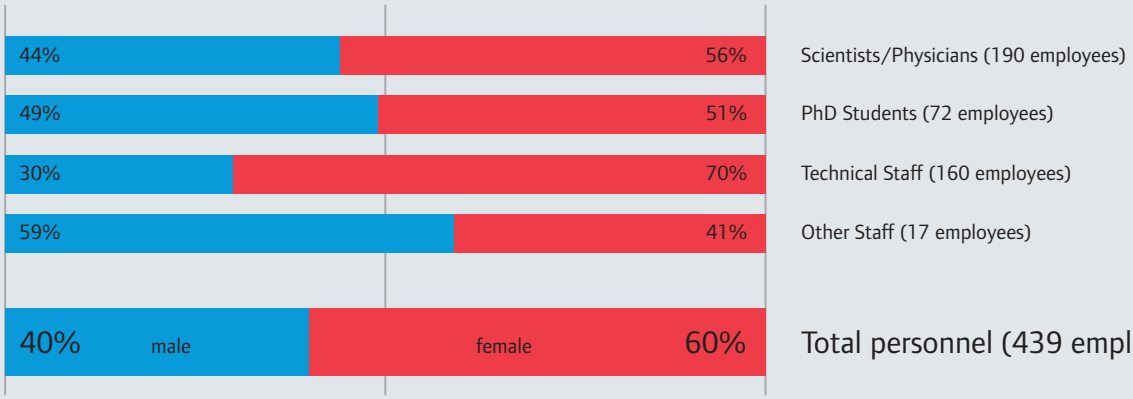



Personnel and Gender Equality

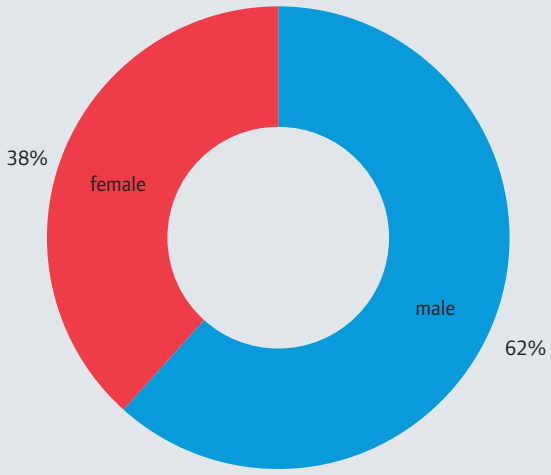



## Personnel and Gender Equality – DZL 2015

In 2015, 439 employees (285.4 Full-Time Equivalents) were directly financed with DZL funds across the five partner centers, an increase of 100 people compared to 2014. Of the 439 funded employees, 263 are women (60%).




Professorships and Leaders of Junior Research Groups




## Professorships and Leaders of Junior Research Groups

In 2015, there were 13 professorships and leaders of junior research groups funded within the DZL, 5 of them women (38%).

## Masthead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