



Deutsches Zentrum für
Lungenforschung

DZG DEUTSCHE ZENTREN
DER GESUNDHEITSFORSCHUNG

German Center for Lung Research

ANNUAL REPORT



2016



Translational Research to Combat Widespread Lung Diseases

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Foreword



Prof. Dr. Werner Seeger
Chairman of the Board



Prof. Dr. Marcus Mall
Board Member



Prof. Dr. Klaus F. Rabe
Board Member



Prof. Dr. Erika v. Mutius
Board Member



Prof. Dr. Tobias Welte
Board Member

We are delighted that this Annual Report of the German Center for Lung Research (DZL) you are holding in your hands is an anniversary edition. This is especially relevant with regard to the many years that are, as a rule, necessary to develop medications and therapies, since a fifth anniversary is often known as “wooden”. We are therefore all the more proud that we can already look back on many significant successes that the DZL scientists have been able to achieve for lung patients since 2011: the development of a novel drug substance to combat allergic asthma, the first available therapy for a life-threatening form of pulmonary hypertension, innovative paths towards an implantable lung as well as great strides in the early detection and treatment of cystic fibrosis – to name but a few examples. Over the past five years, the DZL has been able to contribute to the improvement and expansion of the spectrum of treatment possibilities in each of the eight disease areas it covers. We would like to invite you to acquaint yourselves in the following pages with the DZL’s current developments as well as highlights from our research year 2016.

Despite these initial successes, for many airway diseases there are still only therapies available that offer symptomatic relief, not cause-related curative treatment. Airway diseases like pulmonary infections (primarily pneumonia and tuberculosis, lung cancer and chronic obstructive lung disease (COPD) were responsible for 10 million deaths in 2015 – one-sixth of the deaths worldwide. In the 28 countries of the European Union alone, the total costs incurred due to airway diseases, consisting of direct and indirect costs (for example due to production losses), were estimated to be at least 380 billion euros per year, posing an enormous challenge to our health system.

Thus, joint innovative translational lung research to combat widespread lung diseases is and will continue to be of prominent social interest. Our mutual steps towards improved treatment possibilities will be facilitated by the magnificent work carried out by the scientists at DZL, for which we are extremely grateful! With this momentum behind us, we can look forward to the challenges yet to come and hope that you will continue to accompany us in this important task in the years to come.

The Board of the German Center for Lung Research

About the DZL: Science – Translation in the Focus of Research

Founded in late 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). The DZL is supported by the German Ministry of Education and Research (Bundesministerium für Bildung und Forschung – BMBF) and the States in which each of the sites are located. Leading scientists and clinicians in the field of pulmonary research work together to develop new and innovative therapies for patients with lung disease.

Currently, over 230 principal investigators and their research groups work together to combat respiratory disease through translational research. Twenty-eight leading German research institutions at five sites cooperate in this work: Airway Research Center North (ARCN, Borstel, Grosshansdorf, Kiel and Lübeck), Biomedical Research in Endstage and Obstructive Lung Disease Hannover (BREATH, Hannover), Comprehensive Pneumology Center Munich (CPC-M, Munich), Translational Lung Research Center Heidelberg (TLRC, Heidelberg), and the Universities of Giessen and Marburg Lung Center (UGMLC, Giessen, Marburg and Bad Nauheim).

Research efforts in the DZL are focused on eight Disease Areas: Asthma and Allergy, Chronic Obstructive Pulmonary Disease, Cystic Fibrosis, Pneumonia and Acute Respiratory Distress Syndrome (ARDS), Interstitial (Diffuse Parenchymal) Lung Disease, Pulmonary Hypertension, End-Stage Lung Disease, and Lung Cancer. In each of these disease areas, the entire “bench-to-bedside” translational research chain is applied. Basic scientific findings are applied to the design and implementation of clinical trials and patient care, whilst clinical needs become the scientific questions tackled by DZL scientists. The close cooperation of basic scientists and clinicians is integral to the success of the DZL and is facilitated by regular meetings, symposia, and common infrastructures. Furthermore, many investigators belong to more than one Disease Area team, allowing cross-fertilization of ideas and findings across the research areas.



Asthma and Allergy

Scientific Coordinators of the Disease Area

Prof. Dr. Heinz Fehrenbach (ARCN)

Prof. Dr. Dr. h.c. Erika von Mutius (CPC-M)

Administrative Coordinator of the Disease Area

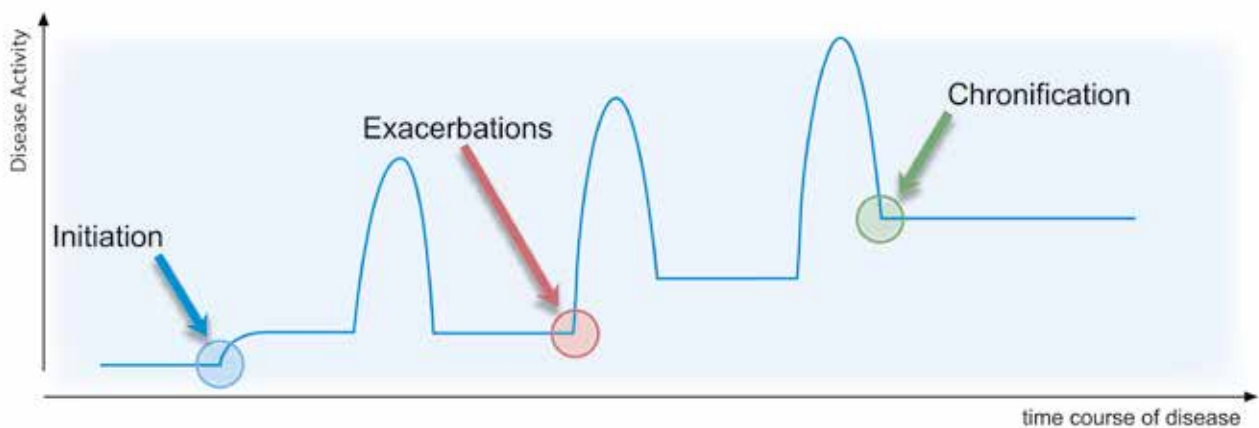
Dr. Jörn Bullwinkel (ARCN)

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 DZL Disease Area Asthma and Allergy.



Focus Areas of Cooperative Projects Integrating Clinical and Basic Research



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

Goals for 2016

Basic Science Flagship Project

- ▶ Impact of allergen-lipid association on sensitization and asthma phenotype development

Translational Flagship Project

- ▶ Role of interleukin-37 (IL-37) and inflammasome regulation in asthma pathogenesis

Clinical Flagship Project

- ▶ From early beginnings to chronic disease: the DZL asthma cohort

Work Package 1: Development of asthma phenotypes: predictors and mechanisms

- ▶ Analysis of biosamples and data from the DZL asthma cohort for validation of clinical asthma phenotypes as well as correlation with specific molecular phenotypes
- ▶ Investigation of endogenous and exogenous factors that determine initiation and progression of asthma phenotypes
- ▶ Identification of biomarkers and targets that allow early prediction of course of disease and development of novel strategies for prevention and personalized therapies

Work Package 2: Risk factors and mechanisms of exacerbations

- ▶ Individuals at risk for exacerbations can be identified by clinical and molecular biomarkers
- ▶ Mechanisms underlying exacerbation can be modeled in vitro and in vivo

Work Package 3: Mechanisms of chronicity and models of intervention

- ▶ Common mechanisms of chronicity among chronic airway diseases: linking asthma and COPD
- ▶ Targets for intervention: identification and validation of mechanisms and target structures in biomaterials and cohorts
- ▶ Development of intervention strategies modifying chronicity processes: proof-of-concept in preclinical models

Research Highlight 2016

How D-tryptophan from bacteria mitigates asthma symptoms

The World Health Organization estimates that about 300 million people suffer from asthma. Many patients with access to a functioning health care system can control their asthma symptoms well by using appropriate medication. Nevertheless, to date asthma can neither be prevented nor cured. In a recent study, DZL scientists tested an alternative approach: if substances that are known to impact positively on the immune system can be isolated from probiotic bacteria, then these may be applied successfully in asthma prevention.

The current research opinion in this area is rather inconsistent: Although there are some encouraging results from first clinical studies with nutritional components such as probiotic bacteria, there is no proof that they can positively influence asthma or other chronic inflammatory diseases. This may be explained in part by the fact that probiotics taken orally encounter a very complex network of microbes and immune cells in the human body. The gut environment shows a high individual diversity – even in healthy subjects – which complicates the interpretation of study results.

Scientists at the DZL sites CPC-M and ARCN tried to reduce this complexity by isolating single substances from probiotic bacteria with a defined influence on the immune system. In a series of experiments human immune cells were treated with supernatants from probiotic bacterial cultures. These supernatants comprised substances secreted by the bacteria. In a next step, two bacterial strains were isolated, which diminish the so-called T_H2 immune response that promotes the allergic airway reaction. Subsequently, the supernatants were fractionated, in order to find out, whether a single substance is responsible for the observed effect. Indeed, this was the case: the bacterial amino acid D-tryptophan was shown to modify the T_H2 response of the immune system in a similar fashion to the supernatant from which it was isolated.

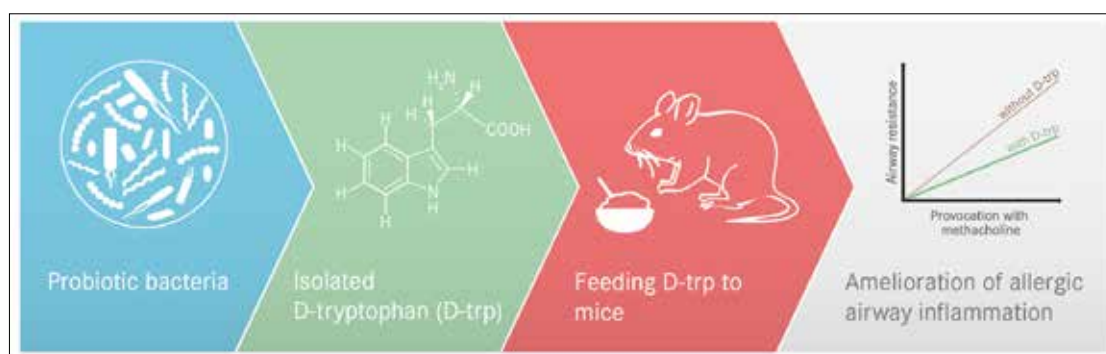
Interestingly, the effects were also observed in mice fed with D-tryptophan. Their cytokine profile – reflecting the immune

reaction – changed comparably to that observed in cell culture. Moreover, the number of so-called eosinophil granulocytes in the lung decreased. These cells are important mediators in asthma. In addition, the reaction of the mice fed with D-tryptophan to an experimental asthma stimulus was less pronounced than that of untreated animals. Unexpectedly, the treatment had also an influence on the gut flora: while diversity of intestinal bacteria is reduced in animals with airway disease in comparison to healthy mice, it improves when diseased animals are fed with D-tryptophan.

The results of the study were published in the *Journal of Allergy and Clinical Immunology*. They support the concept that bacterial compounds can be used to develop prevention strategies for chronic inflammatory diseases such as asthma. Ongoing studies focus on unraveling the cellular mode of action of D-tryptophan. Also, the positive effect on the gut microbiome will be further investigated: the DZL scientists are particularly interested in the question whether a damaged gut flora (e.g. after antibiotic treatment) can regenerate faster after intake of D-tryptophan.

Further information:

Keper I, Fonseca J, Müller C, Milger K, Hochwind K, Kostric M, Fedoseeva M, Ohnmacht C, Dehmel S, Nathan P, Bartel S, Eickelberg O, Schlöter M, Hartmann A, Schmitt-Kopplin P, Krauss-Etschmann S (2017) D-tryptophan from probiotic bacteria influences the gut microbiome and allergic airway disease. *J Allergy Clin Immunol* 139: 1525-1535 (ARCN, CPC-M)



Scientists from the DZL sites CPC-M and ARCN isolated the amino acid D-tryptophan as an effective component from probiotic bacteria and fed it to mice. Subsequent provocation tests using the test substance methacholine resulted in improvement of the symptoms of the allergic airway inflammation due to the feeding with D-tryptophan. In addition, the diversity of the gut microbiome was also improved.

Chronic Obstructive Pulmonary Disease (COPD)

Scientific Coordinators of the Disease Area

Prof. Dr. Klaus F. Rabe (ARCN)

Prof. Dr. Claus F. Vogelmeier (UGMLC)

Administrative Coordinator of the Disease Area

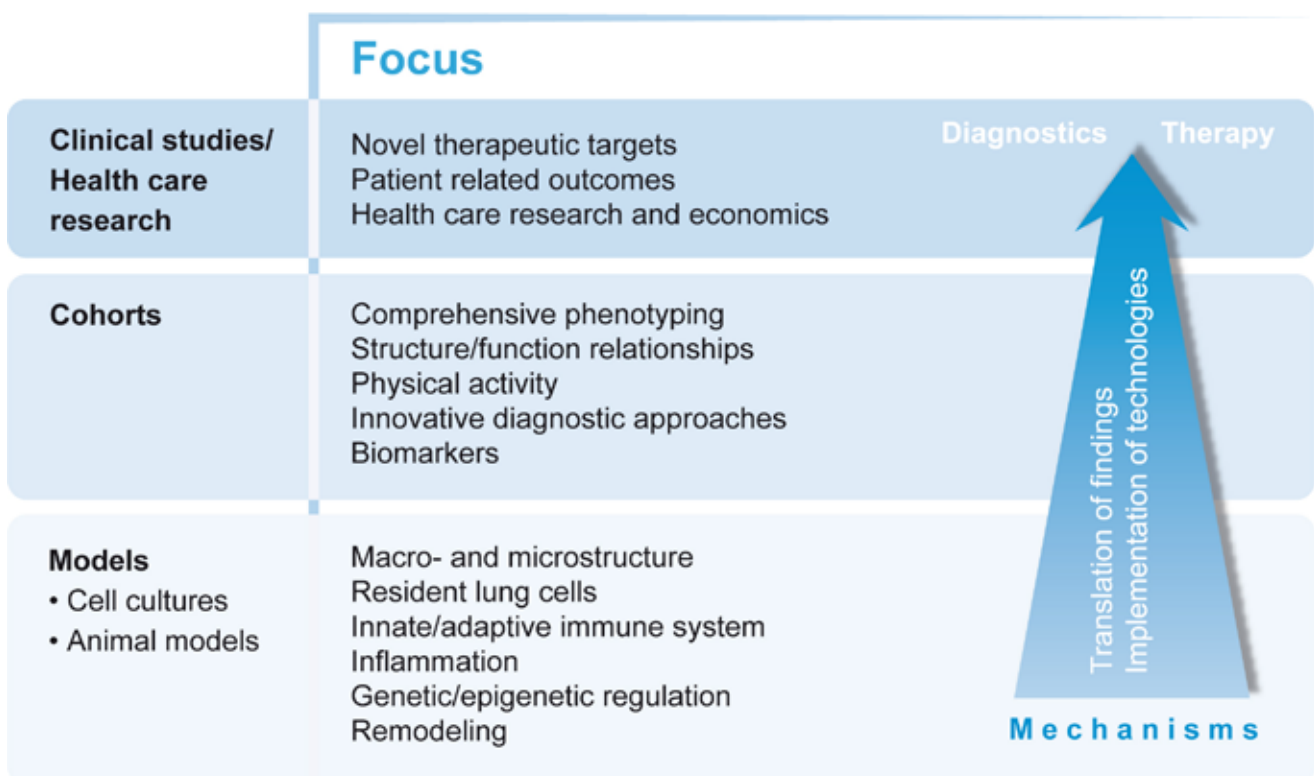
Dr. Jörn Bullwinkel (ARCN)

Participating DZL Partner Sites

All

Chronic Obstructive Pulmonary Disease (COPD) is characterized by a progressive and largely irreversible restriction of lung function. Shortness of breath, the most often observed symptom of COPD, contributes significantly to the decrease in the quality of life of many patients. Although COPD can, to a certain extent, be avoided, the disease is the fourth most frequent cause of death worldwide. The main causes of this disease are smoking and air pollution.

COPD combined with an emphysema is the most frequently occurring destructive lung disease. The loss of structural integrity and the lung's ability to regenerate are critical factors for the course of the disease and therapeutic success; the basic mechanisms are, however, hitherto hardly known. The long-term aim of the DZL research in this area is to translate new therapy concepts based on mechanisms into effective treatment 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 2016

Basic Science Flagship Project

- ▶ Investigation of differential contribution of fibroblast subtypes to (neo-)alveolarization – Exploitation for novel treatment concepts of bronchopulmonary dysplasia (BPD) and COPD

Translational Flagship Project

- ▶ Role of soluble guanylate cyclase (sGC) signaling in smoke-induced airway injury/emphysema and responsiveness to cyclic guanosine monophosphate (cGMP) enhancing therapies

Clinical Flagship Project

- ▶ Deep phenotyping of COPD using imaging and biomarker correlation

Work Package 1

- ▶ Elucidation of molecular mechanisms of remodeling, regeneration and repair in COPD animal models and patient tissues and validation of candidate genes as targets for novel therapeutic strategies

Work Package 2

- ▶ Identification and validation of (further) biomarker candidates, imaging phenotypes and fingerprints, e.g. volatile organic compound markers, magnetic resonance imaging (MRI), Förster resonance energy transfer (FRET) sensors, RNA and methylome patterns

Work Package 3

- ▶ Development, clinical implementation of endoscopic technologies and devices for COPD, e.g. optical coherence tomography (OCT), microsampling probes as well as evaluation of endoscopic lung volume technologies

Work Package 4

- ▶ Exacerbation as overarching topic between four Disease Areas – Development of harmonized study protocols and identification of predictors of disease progression

Work Package 5

- ▶ Investigation of the impact of physical activity on development and progression of COPD and its comorbidities, and on biomarkers of aging, inflammation and remodeling

Work Package 6

- ▶ Utilization of COSYCONET and longitudinal reference cohorts (SHIP, KORA, National Cohort, BeoNet Registry) for a better understanding of respiratory health and COPD prevalence in Germany (natural course in early stages, the consequences of the disease as well as the timing of personalized interventions) – Cross-sectional and longitudinal evaluations

Work Package 7

- ▶ Assessment of health care, patient outcomes and costs in order to support effective and cost-effective management of COPD patients

Research Highlight 2016

Lung function and COPD – what is the genetic influence?

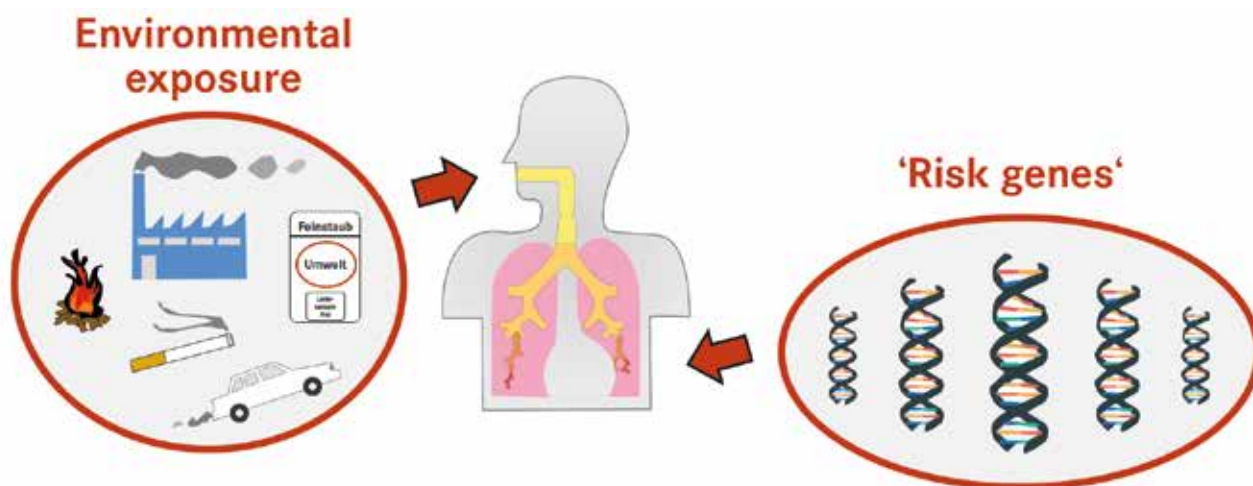
Patients with Chronic Obstructive Lung Disease (COPD) suffer from a continuing decline in lung function. In COPD, permanently inflamed airways cause symptoms such as coughing, expectoration and shortness of breath during physical activity. Therefore, many patients become fatigued more quickly when exercising. The World Health Organization estimates that COPD will be the third most frequent cause of death in 2020.

Risk factors for COPD include both a person's genetic makeup and environmental exposures, such as tobacco smoke and air pollution. As tobacco smoke is the biggest risk factor, by far the best way to prevent COPD is to quit smoking. However, there are some smokers that do not develop COPD and also rare cases of non-smokers who develop COPD. This clearly underlines that genetic factors play an important role in disease initiation and progression. In order to identify and determine the contribution of these factors, an international consortium (including epidemiologists from the DZL site CPC-M) investigated whether impaired lung function is linked to dis-

tinct genetic variants. For this, they performed a so-called genome-wide association study (GWAS) in large population cohorts from several countries.

Based on this large-scale approach, 43 new candidate genes were found to significantly distinguish between good and poor lung function. Also, 54 candidate genes from previous, but much smaller studies were confirmed. Further calculations showed that persons carrying these 'risk genes' for poor lung function have an up to 3.7-fold higher risk of developing COPD. Research on exacerbations, acute aggravations which often lead to hospitalization, found no genetic background. Therefore, other mechanisms must be responsible for exacerbations.

Of particular interest are 'risk genes' and their function in the human body. Some of the genes identified in this study had been linked to other – mostly chronic inflammatory – conditions in earlier studies: examples are the inflammatory bowel diseases ulcerative colitis and Crohn's disease. Other genes



Along with environmental pollutants like contaminated air and cigarette consumption, human genes also influence the occurrence and course of COPD. In a new study, 43 further genes were identified that are jointly responsible for impaired lung function.

show a connection to autoimmune disorders. Interestingly, some of the 97 genes are linked to lung development in early childhood, thus they may also predict adult lung function and risk of developing chronic lung disease.

Findings like these improve our understanding of how the functions of specific genes influence initiation and progression of disease. In individual cases, this can be important for predicting disease outcome. Importantly, clinical drug development may also benefit from genome-wide association studies: even though the COPD genes identified in this study have to be characterized further, results, so far, may help to explore new targets for drug development. Thus, at least a part of the COPD symptoms might be mitigated in future.

Jonsson S, Thorleifsson G, Jonsdottir I, Gislason T, Stefansson K, Schurmann C, Nadkarni G, Bottinger EP, Loos RJ, Walters RG, Chen Z, Millwood IY, Vaucher J, Kurmi OP, Li L, Hansell AL, Brightling C, Zeggini E, Cho MH, Silverman EK, Sayers I, Trynka G, Morris AP, Strachan DP, Hall IP, Tobin MD (2017) Genome-wide association analyses for lung function and chronic obstructive pulmonary disease identify new loci and potential druggable targets. *Nat Genet* 49: 416-425 (CPC-M)

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Cystic Fibrosis (Mucoviscidosis)

Scientific Coordinators of the Disease Area

Prof. Dr. Marcus Mall (TLRC)

Prof. Dr. Dr. Burkhard Tümmler (BREATH)

Administrative Coordinator of the Disease Area

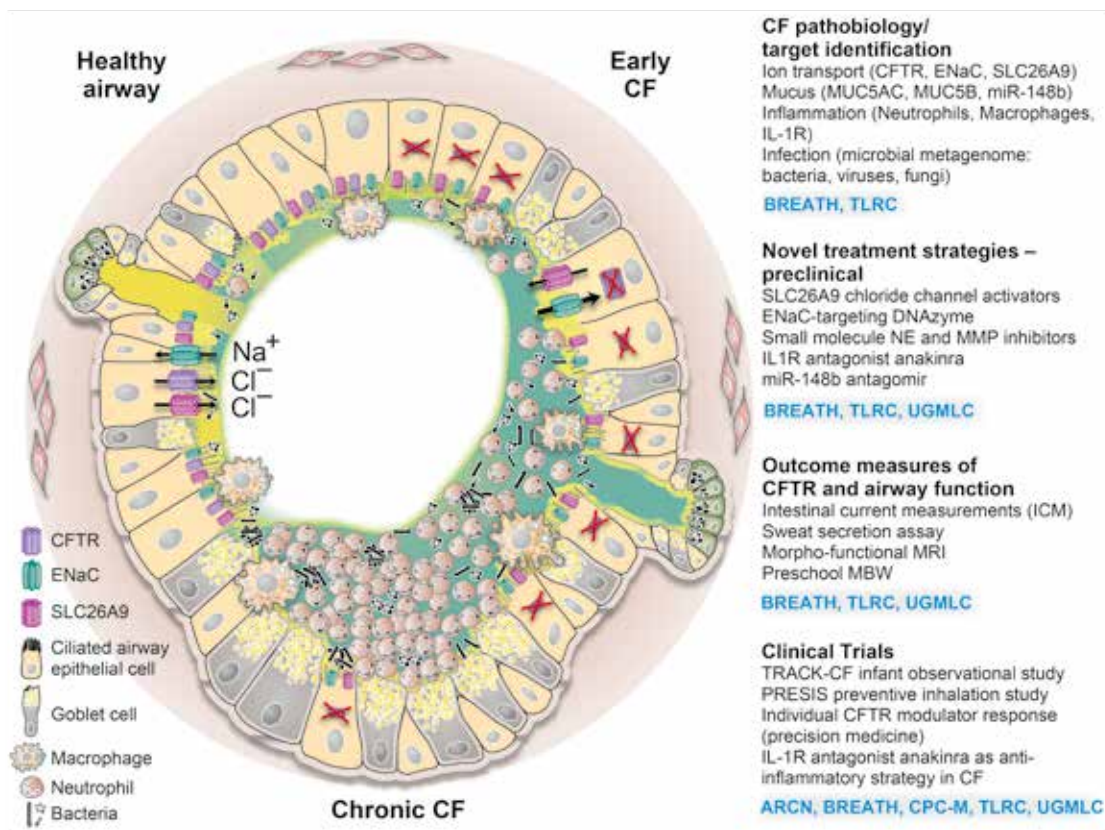
Dr. Birgit Teucher (TLRC)

Participating DZL Partner Sites

ARCN, BREATH, TLRC, UGMLC

Cystic Fibrosis (CF) is the most common genetically determined, early onset and still lethal 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, to develop more sensitive tools for monitoring of disease activity, and 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 2016

Basic Science Flagship Project

- ▶ Characterization of the alternative chloride channel SLC26A9 as a modifier and novel therapeutic target of Cystic Fibrosis.

Translational Flagship Project

- ▶ Elucidation of the pathogenetic role of the microbial metagenome (genetic information contained in the microbiome) in Cystic Fibrosis (CF) lung disease.

Clinical Flagship Project

- ▶ Randomized, double-blind, controlled studies on safety and efficacy of preventive inhalation of hypertonic saline in infants with Cystic Fibrosis (PRESIS) – open label extension trial (NCT01619657).

Work Package 1

- ▶ Identify and validate CF modifiers and novel therapeutic targets in animal models and patient cohorts. Previously identified candidate targets will be evaluated based on retrospective and prospective assessments of survivor effects and lung disease severity.

Work Package 2

- ▶ Elucidate role of CFTR (Cystic Fibrosis Transmembrane Conductance Regulator) chloride channel in non-epithelial host defense mechanisms that protect from infections.

Work Package 3

- ▶ Use established preclinical pipeline for evaluation of novel therapeutic strategies (e.g. DNAzymes, small molecule proteasome inhibitors, miR-148b) targeting epithelial ion transport, mucus and inflammation.

Work Package 4

- ▶ Use and refine quantitative imaging methods of lung structure and function as well as sensitive measures of CFTR function (sweat test, intestinal current measurement (ICM)) for implementation of personalized medicine approaches with emerging CFTR modulators
 - › Clinical Study to determine individual treatment response on CFTR function in patients with F508del mutation with a CFTR modulator therapy (lumacaftor/ivacaftor)

Work Package 5

- ▶ Expand biomaterial collection (DNA, RNA, serum, airway samples, airway and intestinal tissues) of multi-center pediatric and adult CF patient cohorts for deep phenotyping and other studies within the DZL research program.

Research Highlight 2016

The cystic fibrosis lower airways microbial metagenome

The human microbiome consists of myriads of microbes which colonize our skin and all mucosal surfaces. The composition of the bacterial microbiome is typically assessed by partial fragment sequencing of the ribosomal 16S rDNA gene. However, this analysis yields no quantitative data and very often medically relevant bacteria can only be differentiated up to the genus level. Thanks to the emergence of second- and third-generation sequencing technologies and the dramatic fall in sequencing costs the high-throughput sequencing of the microbial metagenome has become a technically and financially feasible alternative. Ten nanograms of genomic DNA are sufficient to quantitatively resolve the composition of microbial communities. Deep sequencing identifies DNA viruses, bacteria, molds and fungi, recognizes the individual strains of the dominant species, pinpoints mutations in pathogenicity factors and antimicrobial resistance determinants and provides information about the metabolic capacity of the microbial gene pool. DZL researchers from the disease area Cystic Fibrosis have set up a pipeline to analyze the microbial metagenome of human airways.

Chronic airway infections determine the course and prognosis of most patients with Cystic Fibrosis (CF). *Haemophilus influenzae* and *Staphylococcus aureus* are typically detected in respiratory secretions during childhood, but later in life *Pseudomonas aeruginosa* and in rare cases *Burkholderia cepacia* complex or atypical mycobacteria become the dominant pathogens in CF lungs.

Researchers of the DZL have investigated the microbial metagenome of the lower CF airways. Typically several dozens of viruses, molds and fungi and hundreds of bacterial species were identified in the patient's respiratory secretions. *Rothia*, *Streptococcus*, *Veillonella* and *Prevotella* were the most prominent genera besides the common staphylococci and pseudomonads. The patient's individual metagenome was stable over time. Within a 2-year period we did not observe any substantial change in the composition of the metagenome unless a pathogen such as *Burkholderia multivorans* had been eradicated by targeted antimicrobial chemotherapy. Bacterial load particularly of staphylococci and pseudomonads increased during acute pulmonary exacerbations, but the overall spec-

trum of microbes remained more or less constant. However, concurrently new mutations emerged in antimicrobial susceptibility loci. Interestingly, these mutations often did not occur in the bacterial targets of treatment but in species of the normal microflora (commensal flora).

The bacterial metagenome mirrored the patient's status of lung health. Healthy patients with normal lung function were harboring a microbial metagenome indistinguishable from that of healthy non-CF controls (see Figure). Since normal airway metagenomes were even observed in a number of young adults we end to conclude that optimal personalized treatment and adherence can sustain healthy CF lungs for many years. On the other hand, a CF-typical microbial metagenome of low diversity dominated by *S. aureus* or *P. aeruginosa* was seen in patients with compromised lung function (FEV1 < 50% predicted) (see Figure). A different scenario was observed in patients with subnormal lung function in the intermediate range (50% < FEV1 < 90% predicted). Each patient showed a distinct microbial metagenome of pathogens, commensals and harmless microbes. These data suggest that during the initial stage of the CF lung disease when local foci of inflammation and remodeling emerge, the CF lungs become colonized with an individual signature of germs. Later on the CF-typical pathogens such as *S. aureus* und *P. aeruginosa* take over and become the dominant bacteria in the microbial community.

In summary, metagenome sequencing can generate quantitative and unbiased data about the microbial diversity in CF lungs, which in future could assist our management of respiratory tract infections in CF.

Further information:

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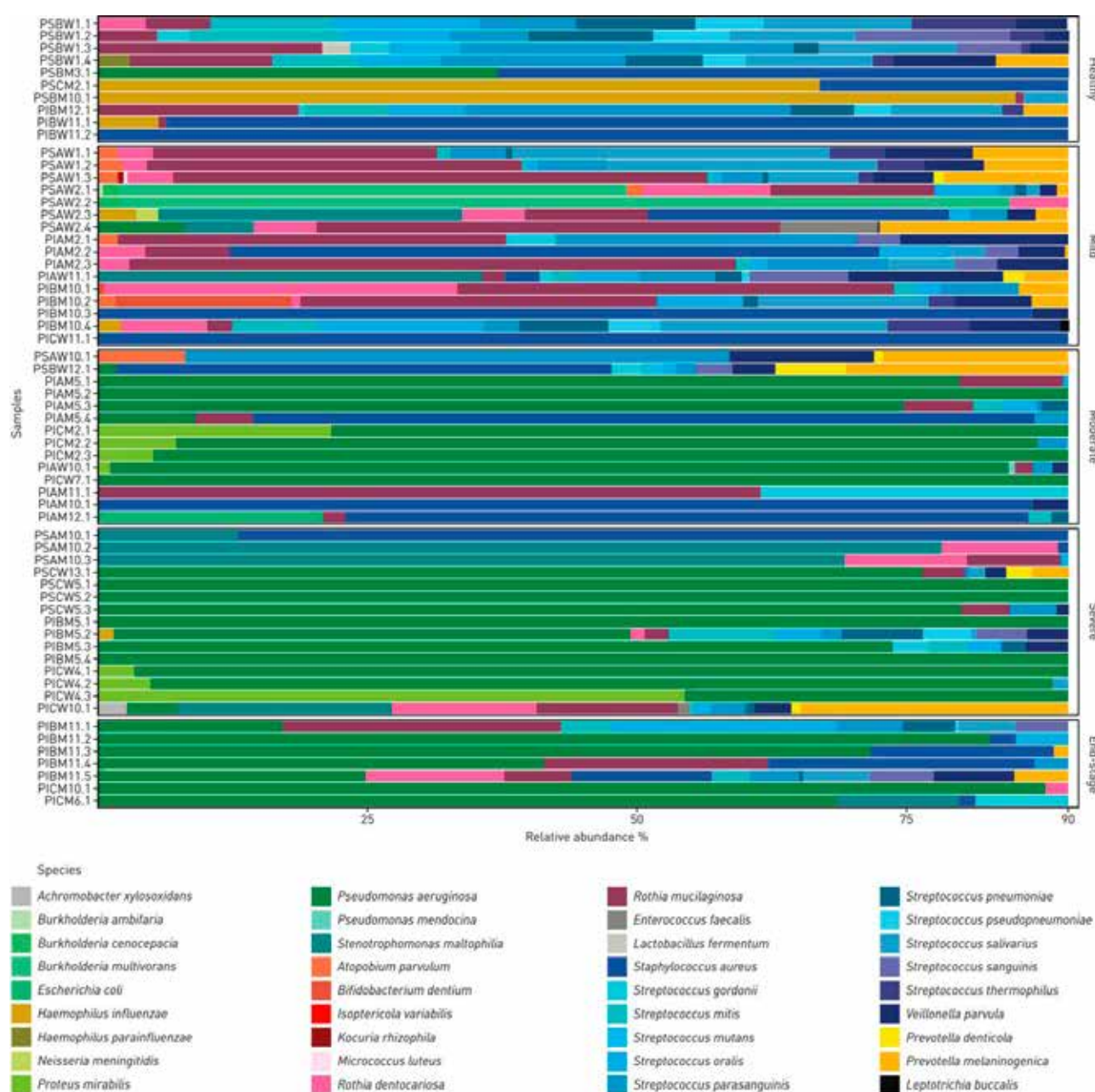


Figure: Composition of microbial communities in induced sputa of (from left to right) healthy, mildly, moderately, severely or very severely (end-stage lung disease) affected individuals with CF. Data are presented in a stacked bar chart of relative abundance as fractions of total reads (y-axis) of the top 90% of species for each patient (x-axis). The color key indicating these species is shown at the right hand side of the figure. Classification of CF patients' disease severity: Healthy CF subjects had normal anthropometry (body mass index > 19) and normal lung function, i.e. multiple breath nitrogen washout revealed a normal lung clearance index and spirometry yielded FEV1 values of more than 90% predicted. Mildly affected CF patients (category 'mild') exhibited normal anthropometry, an anomalous lung clearance index and FEV1 values of 70%–110% predicted at the day of recruitment. Lung function was chronically compromised for three years or more in all moderately or severely affected CF patients (FEV1 50–70%

predicted, category 'moderate'; FEV1 30–50% predicted in the absence of an acute pulmonary exacerbation, category 'severe'; FEV1 < 30% predicted in the absence of an acute pulmonary exacerbation, category 'end-stage lung disease'). Nomenclature of samples: Each sputum sample received a unique identifier, i.e. the two first letters indicate whether the specimen was retrieved from an exocrine pancreatic sufficient (PS) or exocrine pancreatic insufficient (PI) subject. The third letter identifies the age group of the subject (A, child [8–13 years]; B, adolescent and young adult [18–23 years]; C, adult [> 28 years]). The fourth letter indicates the sex (M, male; W, female). The following numeral specifies the subject within his/her group. The number after the dot is the number of the serial specimen collected over a two-year period. Example: The specimen PSCW5.2 is the second sputum sampled from the exocrine pancreatic sufficient adult CF female 5.

Pneumonia and Acute Lung Injury

Scientific Coordinators of the Disease Area

Prof. Dr. Jürgen Lohmeyer (UGMLC)

Prof. Dr. Tobias Welte (BREATH)

Administrative Coordinator of the Disease Area

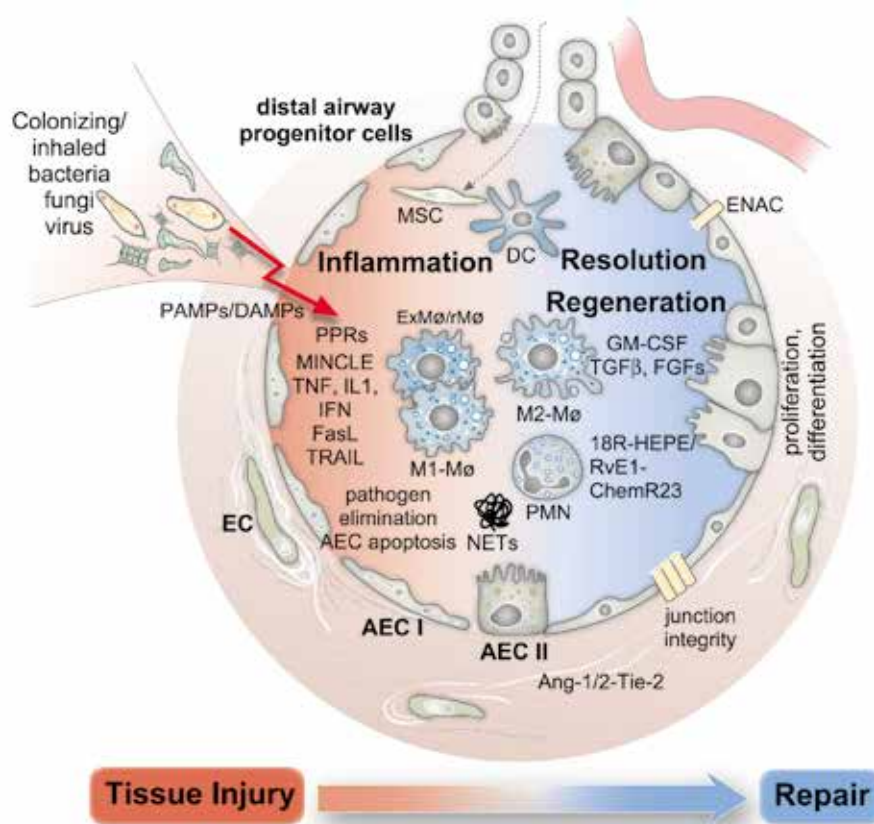
Dr. Sylvia Weißmann (UGMLC)

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 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 (ALI) with severe respiratory failure. The goal of this Disease Area is to decipher the molecular mechanisms underlying the spread of inflammation into the alveoli and to understand the cellular and molecular signaling pathways leading to dissolution of inflammation and repair of the alveolar epithelium integrity. Based on this knowledge, new therapeutic concepts are being developed to attenuate lung tissue damage and promote tissue repair and organ regeneration.



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 2016

Basic Science Flagship Project

- ▶ Nasopharyngeal colonization approaches as preventive strategies against invasive pneumococcal disease
- ▶ *Streptococcus pneumoniae* (Spn), a common bacterium of nose and mouth, but at the same time the most prevalent pathogen in community-acquired pneumonia, can also confer immunological protection against invasive pneumococcal disease. DZL aims to characterize these yet unclear host-defense mechanisms and use the results for the development of novel preventive strategies.

Translational Flagship Project

- ▶ Targeting regeneration programs and cellular interactions in lung stem cell niches for repair after infection-induced injury
- ▶ Induction and promotion of stem/progenitor cell activity with inhaled growth factor preparations or other molecular compounds of the local (lung) epithelial stem/progenitor cell signaling networks in pre-clinical models – establishment of optimized dose and time schedules
- ▶ Development of stem-cell derived cell therapy concepts, proof-of-concept preclinical studies

Clinical Flagship Project

- ▶ Systematic analyses of granulocyte-macrophage colony-stimulating factor (GM-CSF) induced host defense and repair signatures in alveolar and circulating innate immune cells from patients included in the GI-HOPE study (GI-HOPE-SIG)
 - › Identification of biomarkers related to GM-CSF therapy (response predictive)
 - › Mechanistic insights into GM-CSF effects (identification of potential new pathways offering for novel targets)

Work Package 1

- ▶ Role of cell-intrinsic pattern (microbes, damage) recognition receptor (PRR) signaling cross talk in shaping lung immune responses
- ▶ Signal integration and resulting gene regulatory events determining quality and quantity of the host immune response (e.g. discrimination between pathogens and commensal microbes)
- ▶ Pathogen evasion strategies to circumvent/exploit host defenses

Work Package 2

- ▶ Cell-specific in-vivo/vitro analysis and network biology of lung inflammation – initiation/control/ termination/resolution during infection
 - › How do immune cells and “general” lung tissue communicate at the molecular level during disease development and resolution/healing?
 - › What role do populations of macrophages play in lung injury and repair, which differ with respect to their polarization, ontogeny, gene editing and response to tissue specific signals?
 - › Contribution of dendritic cells and their products
 - › Role of resolvin E1 and related lipid mediators in termination/resolution of inflammation in pneumonia

Work Package 3

- ▶ Preclinical evaluation of targeted and spatially/temporally restricted interventions to attenuate alveolar injury and protect lung barrier function while preserving host defense and repair capacity (e.g. use of lipid mediators or improvement of fluid clearance)

Work Package 4

- ▶ Novel protein-based immunization strategies and non-antibiotic targets for ALI prevention and treatment

Work Package 5

- ▶ Preclinical/clinical development of local-progenitor/stem cell-based ALI repair strategies
 - › Analysis of “native” regeneration programs in various lung stem cells and identification of the cellular interactions (e.g. with mesenchyme or immune cells) in their niches in lung infection models
 - › Mechanisms of pathogen-induced lung tissue regeneration failure and its therapeutic reversal

Work Package 6

- ▶ Phase II/III clinical trials of inhalation based support therapies (GM-CSF; FGF10) and antibiotics in COPD exacerbation – signature analysis in large patient cohorts (CAPNETZ, PROGRESS) to identify novel biomarkers (e.g. miRNAs in broncho-alveolar lavage)

Research Highlight 2016

How pneumococci are recognized in the lung: the Mincle-Glc-DAG axis

Streptococcus pneumoniae (pneumococcus) is the most significant cause of community-acquired pneumonia which, in Germany alone, is diagnosed about 500,000 times each year. Pneumococcal pneumonia is associated with massive damage of the lung tissue. On the cellular level it leads to severe reactions in the defense against infections in the lung and consequently exudate macrophages and neutrophilic granulocytes are recruited into the lung and activated in order to help the resident alveolar macrophages eliminate the pathogens. Conversely, pneumococci also attack defense cells such as alveolar epithelial cells in the lung, which leads to extensive damage in the epithelial lining of the pulmonary alveoli and consequently a developing respiratory insufficiency.

It has been known for many years that bacterial pathogens can be recognized by various forms of pattern recognition receptors (PRR) from host cells which themselves can initiate a specific defense against infections. At the BREATH (Biomedical Research in Endstage and Obstructive Lung Disease Hannover) site of the DZL a new pattern recognition pathway for pneumococci using professional lung phagocytes has been identified. The research work, carried out in cooperation with Kyushu University in Japan, has shown for the first time that pneumococci carry a membranous glycolipid, the so-called glucosyl-diacylglycerol (Glc-DAG), which specifically binds the pattern recognition receptor Mincle (macrophage-inducible C-type lectin) to the cell surface of macrophages and neutrophilic granulocytes.

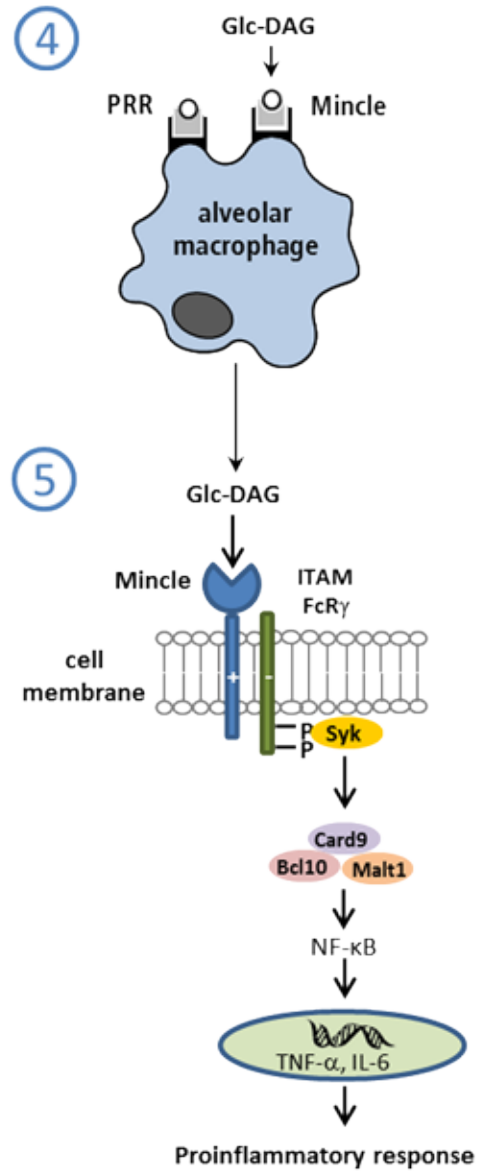
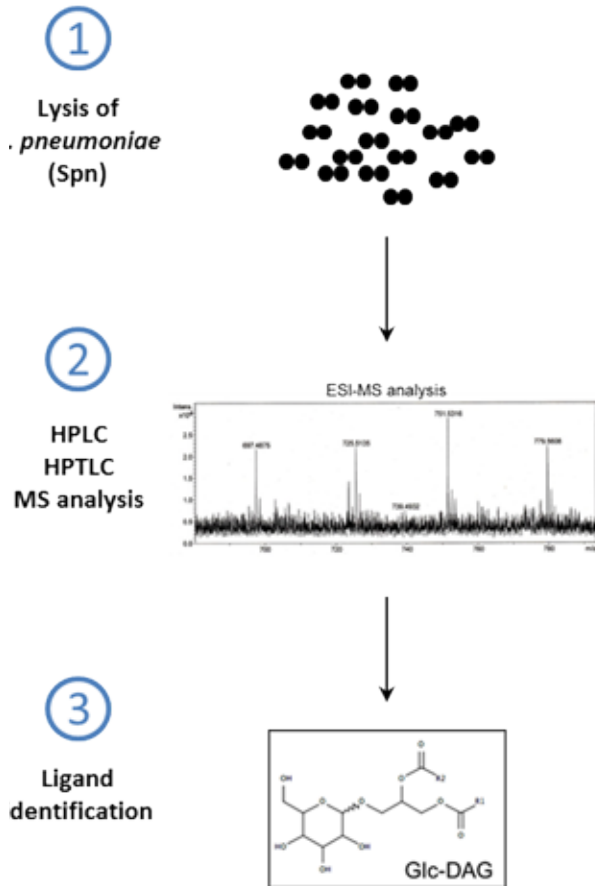
As *in vitro* studies with murine and human alveolar macrophages have shown, the Mincle-Glc-DAG interaction leads to the secretion of pro- and anti-inflammatory cytokines, which are essential for the initiation and limitation of an inflammatory response to bacterial infection. Mincle-deficient macrophages showed no cytokine response to Glc-DAG stimulation and Mincle-deficient mice were highly susceptible to pneumococcal infection. In comparison, chimeric Mincle-KO mice, after exchanging their hematopoietic system for that of wild-type

mice, showed a restored cytokine response as well as a significantly improved defense against infection with pneumococci.

In summary, a new PRR ligand interaction in the host recognition of pneumococci has been successfully identified, whereby new antibiotic-independent starting points for the therapy of pneumococcal pneumonia have emerged.

Further information:

Behler-Janbeck F, Takano T, Maus R, Stolper J, Jonigk D, Tort Tarrés M, Fuehner T, Prasse A, Welte T, Timmer MS, Stocker BL, Nakanishi Y, Miyamoto T, Yamasaki S, Maus UA., (2016) C-type Lectin Mincle Recognizes Glucosyl-diacyl-glycerol of *Streptococcus pneumoniae* and plays a protective role in pneumococcal pneumonia. *PLoS Pathog.* 12:e1006038.



Researchers in the Disease Area Pneumonia and Acute Lung Injury have been successful in identifying a novel mechanism for the recognition of pneumococci through pulmonary host defense cells, whereby new therapeutic options in the treatment of pneumonia will emerge in the future.

Diffuse Parenchymal Lung Disease (DPLD)

Scientific Coordinators of the Disease Area

Prof. Dr. Andreas Günther (UGMLC)

PD Dr. Anne Hilgendorff (CPC-M)

Administrative Coordinators of the Disease Area

Dr. Antje Brand (CPC-M)

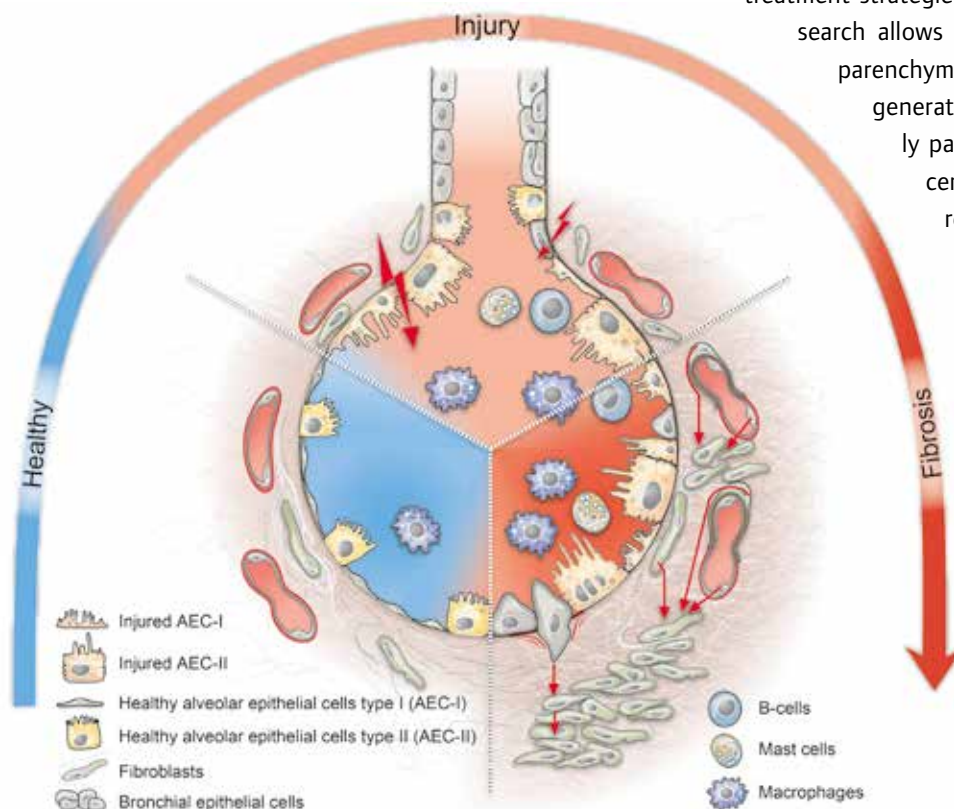
Dr. Jasmin Wagner (UGMLC)

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.

Although different in origin, many DPLD patients share the fate of progressive scarring and poor prognosis. The recently developed and authorized antifibrotic medical treatments are capable of retarding the progression in Idiopathic Pulmonary Fibrosis, but still the only curative option is lung transplantation in suitable cases. This underlines the urgent need for a better understanding and detection of early disease processes. Knowledge about early markers and their use in the clinical setting will allow the implementation of personalized treatment strategies. The German Center for Lung Research allows the comprehensive investigation of parenchymal lung diseases in cohorts spanning generations, from the neonate to the elderly patient. This will enable us to identify central disease mechanisms as well as repair and regeneration strategies and new treatment options.



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 2016

Basic Science Flagship Project

- ▶ Crosslinkage of different, adult and pediatric, registries and biobanks such as e.g. chILD (www.childEU.net; pediatric) and the eurIPFreg (www.pulmonary-fibrosis.net; adult) on the level of the DZL data warehouse.
- ▶ Further description, evaluation and distribution of murine and human ex vivo models of DPLD including bronchopulmonary dysplasia (BPD).
- ▶ Continuous assessment of costs, health-related quality of life and economic viability of new therapeutic approaches.
- ▶ Development of a new clinical study protocol focusing on exacerbations in order to prospectively collect biospecimens from patients with acute worsening due to exacerbation.

Translational Flagship Project

- ▶ Impaired alveolar epithelial surveillance systems and their triggering role in DPLD
- ▶ Interaction of endoplasmic reticulum, proteasome, lysosomal and mitochondrium under conditions of epithelial stress: impact on cellular apoptosis and senescence

Clinical Flagship Project

- ▶ Assessment of epigenetic changes in different cell populations in the fibrotic lung: mesenchymal, epithelial and vascular cells
- ▶ Impact of specific epigenetic changes on the pro-fibrotic phenotype of lung fibroblasts
- ▶ Evaluation of treatment modalities aiming to correct epigenetic programming and lung fibrosis

Work Package 1

- ▶ Further characterization of EMT and lipofibroblast to myofibroblast trans-differentiation and its impact on lung fibrosis
- ▶ Disturbed crosstalk between alveolar macrophages and alveolar epithelial cells: programmed cell removal versus persistence of apoptotic cells
- ▶ (re)-induction of cellular plasticity in epithelial and mesenchymal cells of the diseased lung under consideration of factors with developmental relevance

Work Package 2

- ▶ Assessment of the microbiome, virome and mycobiome in Idiopathic Pulmonary Fibrosis
- ▶ Exacerbation of DPLD: understanding the pro-fibrogenic action of occult or overt respiratory viral infections in an pre-injured alveolar epithelium
- ▶ Defining the role of bacterial respiratory infections in the development of DPDL including BPD
- ▶ Analysis of environmentally relevant factors and their interaction with the lung epithelium and mesenchyme under consideration of epigenetic changes and impairment of the pulmonary regenerative potential

Work Package 3

- ▶ Improved understanding of FGF, PDGF, SHH, Wnt and Notch signaling pathways in the context of DPLDs and assessment of therapeutic potentials
- ▶ Single cell characterization of different pulmonary cell populations in various clinical and experimental conditions of DPLD
- ▶ Definition of the relevant stem cell niches of the lung periphery and the airways contributing to epithelial repair in DPLD

Work Package 4

- ▶ Multiparameter genetic, molecular, imaging and clinical phenotyping of different forms of DPLD and neonatal chronic lung diseases for sub-differentiation, clinical stratification and screening purposes as well as therapy monitoring.
- ▶ Assessment of the therapeutic potential of anti-fibrotic drugs in non-IPF forms of DPLD

Research Highlight 2016

On the plasticity of the pulmonary mesenchyme

Lung Fibrosis is usually a progressive and ultimately fatal event that results in loss of lung function, gas exchange and quality of life. In the most aggressive form of DPLD, the so called Idiopathic Pulmonary Fibrosis (IPF), the mean life expectancy after diagnosis ranges from 2-3 years without treatment. Although there are numerous different forms of Diffuse Parenchymal Pulmonary Diseases (DPLD), many of these share the fate of progressive scarring of the lungs. One pivotal step in the scarring process of the lung is the formation of so-called fibroblast foci, which largely consist of activated myofibroblasts and which represent “hot” areas of active matrix production and deposition as well as parenchymal distortion. For this reason, most of the previously developed drugs that had been under consideration for treatment of DPLD, especially IPF, were all targeting this final scarring event. As the two authorized drugs, however, are still not able to stop the disease, there is a high need for further developments.

In the light of this perspective, it appears logical to better understand the origin of these activated myofibroblasts. Previously, epithelial to mesenchymal transition (EMT) had been suggested to represent one possible mechanism contributing to the expansion of the pulmonary fibroblast population. However, existing data are still controversial if such mechanism truly takes place in clinical IPF and if this would represent a therapeutically druggable process.

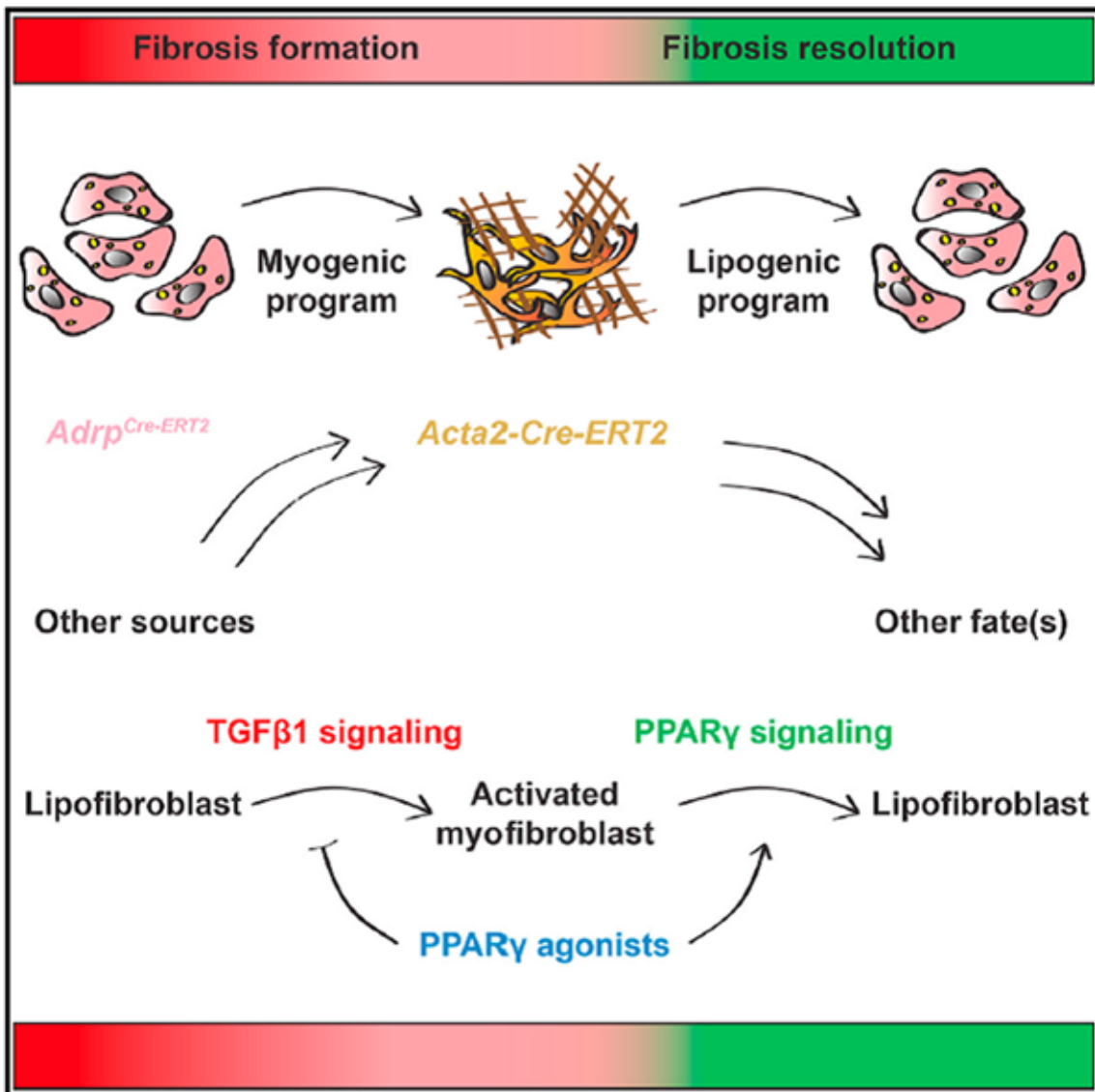
DZL Reseachers have now provided important insights into the possible contribution of the lipofibroblast pool to activated myofibroblast formation under conditions of IPF. The lipofibroblast is a normal cellular component of the healthy adult lung. It usually resides in close proximity to alveolar type II cells (AECII) and is characterized by being rich in lipid droplets. Lipofibroblasts are supposed to “feed” the AECII with lipid precursors, as AECIIs need to produce and recycle large amounts of pulmonary surfactant, the highly active surface tension-reducing lipoprotein film covering our airspaces and making breathing possible at normal transpulmonary pressures. Previous data generated by this group of DZL researchers provided evidence that, during lung morphogene-

sis, lipofibroblasts originate from a FGF10 positive, mesenchymal cell population.

In their current study, multiple transgenic and knock-in mice were used to lineage-trace lipogenic and myogenic populations of lung fibroblasts during the injury and resolution phase of the bleomycin model of lung fibrosis, a common and widely used model of lung fibrosis at this time. Although being not a perfect model of IPF, it offers the advantage of having a pro-fibrotic phase, with active scarring and matrix deposition in the lung, as well as a resolution phase, during which the excessive matrix and cellular populations are removed again. It was found that the resident lipofibroblast population served as a source of activated myofibroblasts during lung fibrosis development. In contrary to the original hypothesis, smooth muscle cells were not found to represent a relevant precursor cell for the activated myofibroblast. Furthermore, the group also observed that one subpopulation of activated myofibroblasts transitioned into a lipofibroblast-like phenotype during the resolution phase. Of importance, therapeutic intervention with the PPAR γ agonist rosiglitazone helped to reinforce the lipofibroblast phenotype and to antagonize the TGF β 1-mediated fibrogenic response in primary lung fibroblasts taken from IPF lungs. This paper therefore greatly expands our current knowledge with regard to the origin of activated myofibroblasts in lung fibrosis and offers novel therapeutic principles for patients with progressive scarring of the lung.

Further information:

El Agha E, Moiseenko A, Kheirollahi V et al., Two-way conversion between lipogenic and myogenic fibroblastic phenotypes marks the progression and resolution of lung fibrosis. *Cell Stem Cell* 20:261-273, 2017, epub 2016



Researchers of the Disease Area Diffuse Parenchymal Lung Diseases (DPLD) have provided important evidence that the activated myofibroblast, the cell type largely responsible for excessive matrix (collagen) production and development of the fibroblast foci, may originate from local resident lipofibroblasts, a cell usually residing in close proximity to alveolar type II cells and involved in pulmonary surfactant synthesis. The DZL scientists also figured out that therapeutic augmentation of the PPAR γ pathway may be helpful in pushing activated myofibroblasts back into a lipofibroblast-like phenotype, which offers novel therapeutic opportunities for patients with the dreadful disease IPF.

Pulmonary Hypertension

Scientific Coordinators of the Disease Area

Prof. Dr. H. Ardeschir Ghofrani (UGMLC)

Prof. Dr. Ralph T. Schermuly (UGMLC)

Administrative Coordinator of the Disease Area

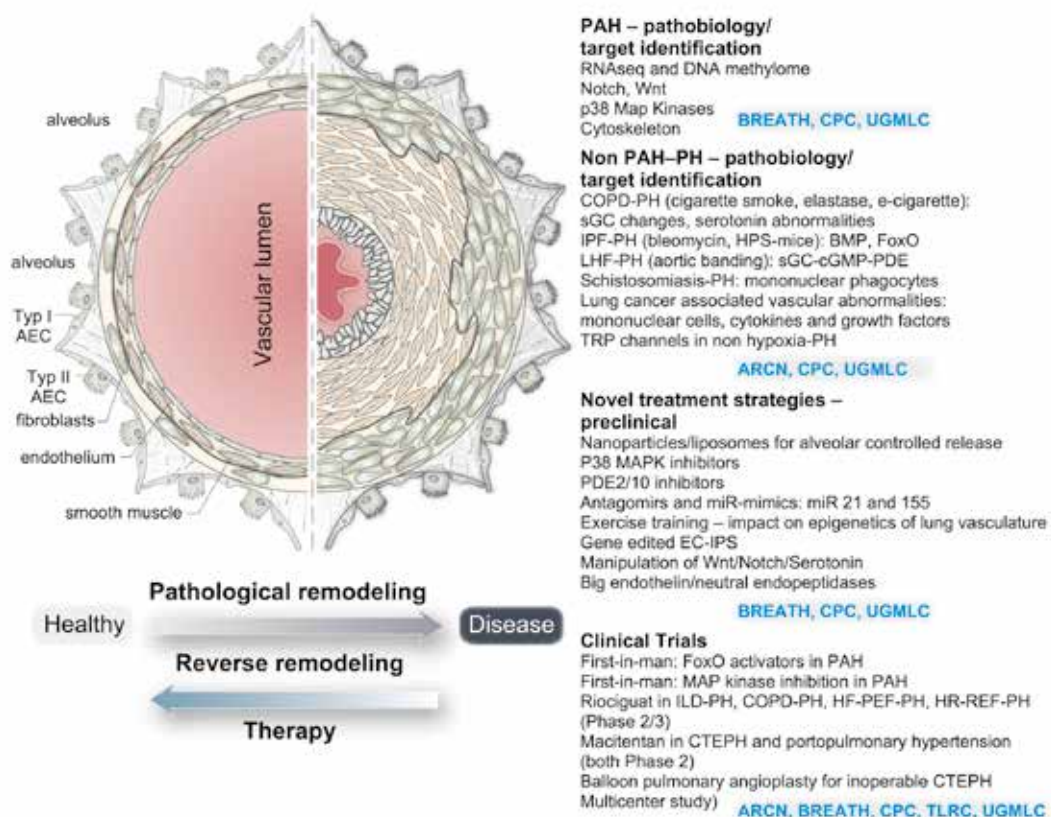
Dr. Sylvia Weißmann (UGMLC)

Participating DZL Partner Sites

All

Pulmonary Hypertension (PH) is a disease of the pulmonary vasculature, leading to shortness of breath, dizziness, fainting, and ultimately right heart failure. This Disease Area is divided into five defined subclasses. Worldwide, a total of approximately 100 million people suffer from one of the forms of Pulmonary Hypertension. The vascular pathology is characterized by vasoconstriction of the pulmonary vessels and abnormal (pseudomalignant) remodeling processes of all vessel layers. An excessive proliferation of the vascular smooth muscle cells (SMC) is a prominent feature in virtually all forms

of the disease. These remodeling processes lead to a severe loss of the cross-sectional area of the vessels, vascular pruning, and a concomitant increase in right ventricular afterload. Current PH therapy provides symptomatic relief and improves prognosis, but falls short with regard to the reestablishment of structural and functional lung vascular integrity that is required for symptom-free long-term survival. The restoration of the vascular structure and function (reverse modeling) is the main goal of the research work carried out by the PH team.



The Disease Area Pulmonary Hypertension focuses on the identification of structures that may serve as 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 2016

Basic Science Flagship Project

- ▶ Evaluation of Wnt/ β -catenin mediated (fibro)-proliferative responses in Pulmonary Hypertension, a molecular pathway associated with embryonic development, cell fate (proliferation/apoptosis) and maintenance of cardiovascular function

Translational Flagship Project

- ▶ Evaluation of MAPK inhibition as novel therapeutic strategy in PH in preclinical models

Clinical Flagship Project

- ▶ Balloon pulmonary angioplasty (BPA) for patients with inoperable or persistent Chronic Thrombo-Embolic Pulmonary Hypertension (CTEPH)

Work Package 1

- ▶ Identification and characterization of key molecular and cellular players driving maladaptive vascular remodeling in Pulmonary Arterial hypertension (PAH)
- ▶ (RNAseq and DNA methylome analysis, exploration of the PAH Notch profile and evaluation of Notch inhibition, profiling p38 MAPK downstream of growth factors, analysis of cytoskeletal changes)

Work Package 2

- ▶ Identification and characterization of key molecular and cellular players driving vascular remodeling in non-PAH forms of PH
- ▶ DPLD associated PH, cigarette smoke and e-cigarette induced pulmonary vascular remodeling, high altitude/hypoxia induced PH, schistosomiasis, lung cancer)

Work Package 3

- ▶ Development and refinement of tailored anti-remodeling, reverse-remodeling and regenerative treatment strategies
- ▶ (Inhalative vasodilatory strategies in PH: nanoparticle- and liposome-based controlled release formulations, novel PDE2/PDE10 inhibitors, big-endothelin, natriuretic peptides, antagomirs/miR-mimics, epigenetics)

Work Package 4

- ▶ Utilization of large scaled biobanks and comprehensive databases for classification and differentiation of different PH varieties with respect to commonalities/differences regarding phenotype and responsiveness to therapy.

Work Package 5

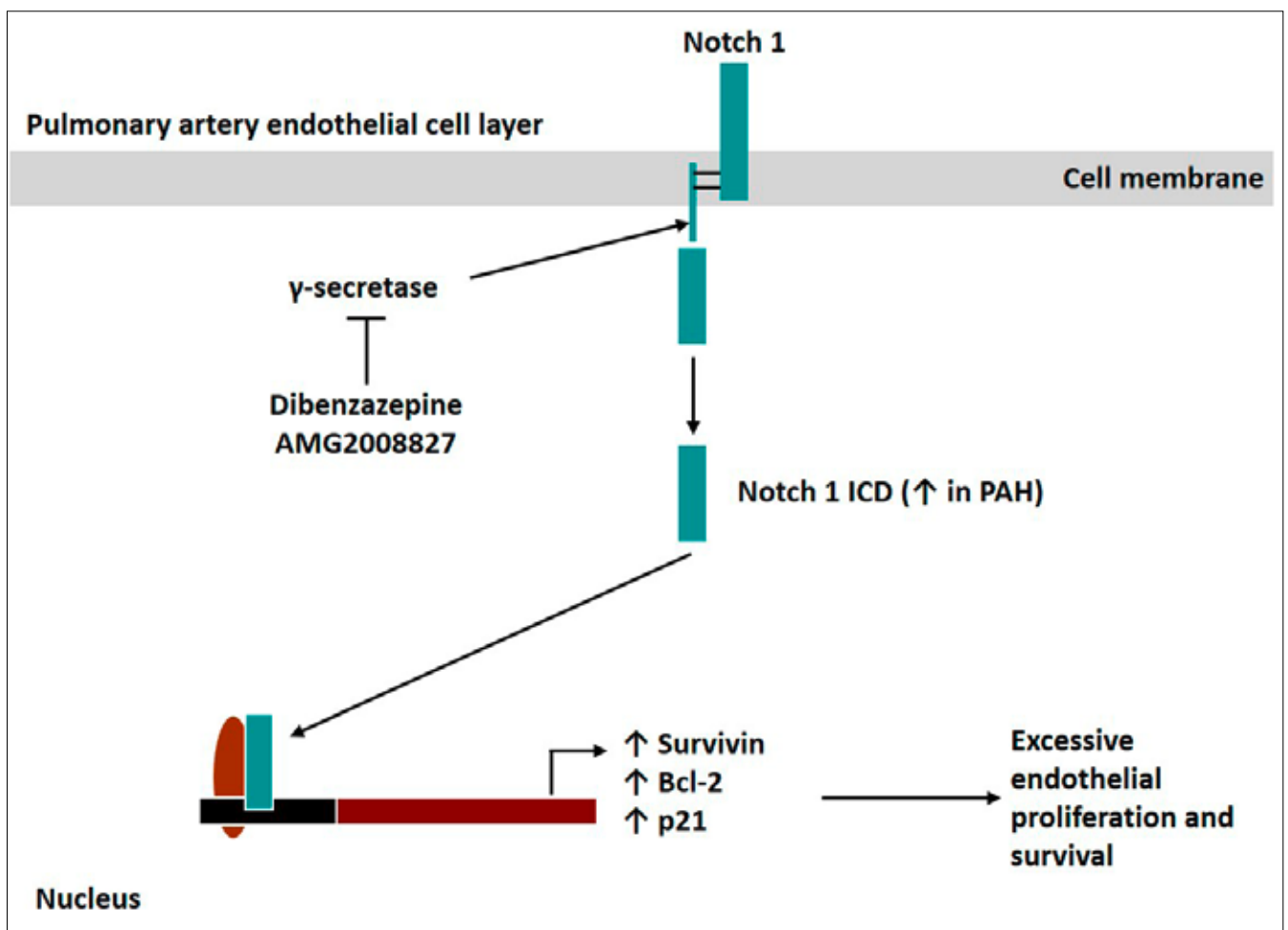
- ▶ Translation into proof-of concept and large scale clinical trials, to improve long-term outcome and allow for individualization of therapeutic strategies
- ▶ (FoxO activators, MAP kinase inhibition, riociguat (phase II/III trials) for treatment of ILD-PH, COPD-PH and other forms, macitentan for treatment of CTEPH and portopulmonary hypertension)

Research Highlight 2016

Notch1 signalling regulates endothelial proliferation and apoptosis in pulmonary arterial hypertension

Notch receptors (Notch1-4) are transmembrane proteins which interact with their ligands expressed on adjacent cell membranes. Binding of the ligand triggers proteolytic cleavage of the Notch receptor by γ -secretase releasing Notch intracellular domain (NICD). NICD translocates to the nucleus inducing the transcription of Notch target genes. These are involved in numerous cellular processes, such as stem cell

maintenance, cell fate specification, differentiation, proliferation and apoptosis. Here, several studies have linked Notch1 signalling to the development and injury of the systemic vasculature but less is known about its role in the lung (e.g. the endothelium) and its contribution in the pathogenesis of PAH (Pulmonary Arterial Hypertension). Therefore, we aimed to analyze the expression and function of Notch1 in endothe-



Notch signalling in Pulmonary Arterial Hypertension (PAH). Schematic representation of the proposed role of Notch signalling in pulmonary vascular remodeling in PAH. Notch1ICD: Notch1 intracellular domain.

lial cells of the pulmonary vasculature as well as its impact on the onset of this life-threatening disease. Lung samples from IPAH (Idiopathic PAH) patients and healthy individuals were received from Giessen University Hospital and investigated for their expression of Notch1 on mRNA, protein and tissue level. Subsequently, an experimental model of PAH was studied to confirm similar findings between the human phenotype and the animal model which (amongst others) shows a characteristic feature of PAH, namely the presence of hyper-proliferative and apoptosis-resistant endothelial cells. This can be seen in rats which develop PAH when they are exposed to hypoxia (reduction of oxygen concentration from 21 to 10%) 3 weeks after injection of the VEGFR-2 inhibitor SU5416. Our results demonstrate an increased expression of Notch1 in the lungs of both Idiopathic PAH (IPAH) patients and hypoxia/SU5416 (SUHx) rats compared with healthy subjects. Further in vitro experiments with isolated PAECs (pulmonary artery endothelial cells) were conducted to decipher the role of Notch1 in this particular cell type. These studies showed that Notch1 increased proliferation of human PAECs (pulmonary arterial endothelial cells) via downregulation of a cell-cycle inhibitor p21 and inhibited apoptosis via two anti-apoptotic proteins, Bcl-2 and Survivin. These results encouraged us to specifically target this pathway by applying a compound which blocks Notch1 action. For that purpose we used the γ -secretase inhibitor Dibenzazepine (DBZ) which prevents proteolytic cleavage of Notch1 (and Notch3) and further NICD signaling in human PAECs. DBZ dose-dependently decreased proliferation and migration of hPAECs. Notably, Notch1 expression and transcriptional activity were increased under hypoxia in hPAECs and knockdown of Notch1

inhibited hypoxia-induced proliferation of the cells. Finally, we tested a well-known γ -secretase inhibitor (AMG2008827) in the hypoxia/SU5416 (SUHx) rat model, to prove its applicability for future therapies of PAH. In vivo treatment with AMG2008827 significantly reduced the right ventricular systolic pressure and right heart hypertrophy in SUHx rats. Here, we conclude that Notch1 plays a critical role in PAH and Notch inhibitors may be a promising therapeutic option for PAH. These data describe a novel pathway involving Notch1 signalling, which regulates a pro-proliferative and pro-survival phenotype in PAECs (see figure). This pathway appears to be further activated by hypoxia stimulation. Both in vitro and in vivo data using pharmacological γ -secretase inhibitors suggest that Notch1 is a potential therapeutic target in PAH.

Further information:

Notch1 signalling regulates endothelial proliferation and apoptosis in pulmonary arterial hypertension. Dabral S, Tian X, Kojonazarov B, Savai R, Ghofrani HA, Weissmann N, Florio M, Sun J, Jonigk D, Maegel L, Grimminger F, Seeger W, Savai Pullamsetti S, Schermuly RT. *Eur Respir J.* 2016 Oct;48(4):1137-1149. doi: 10.1183/13993003.00773-2015. Epub 2016 Jul 28. PMID: 27471204

End-Stage Lung Disease

Scientific Coordinators of the Disease Area

Prof. Dr. Dr. Axel Haverich (BREATH)

Prof. Dr. Veronika Grau (UGMLC)

Administrative Coordinator of the Disease Area

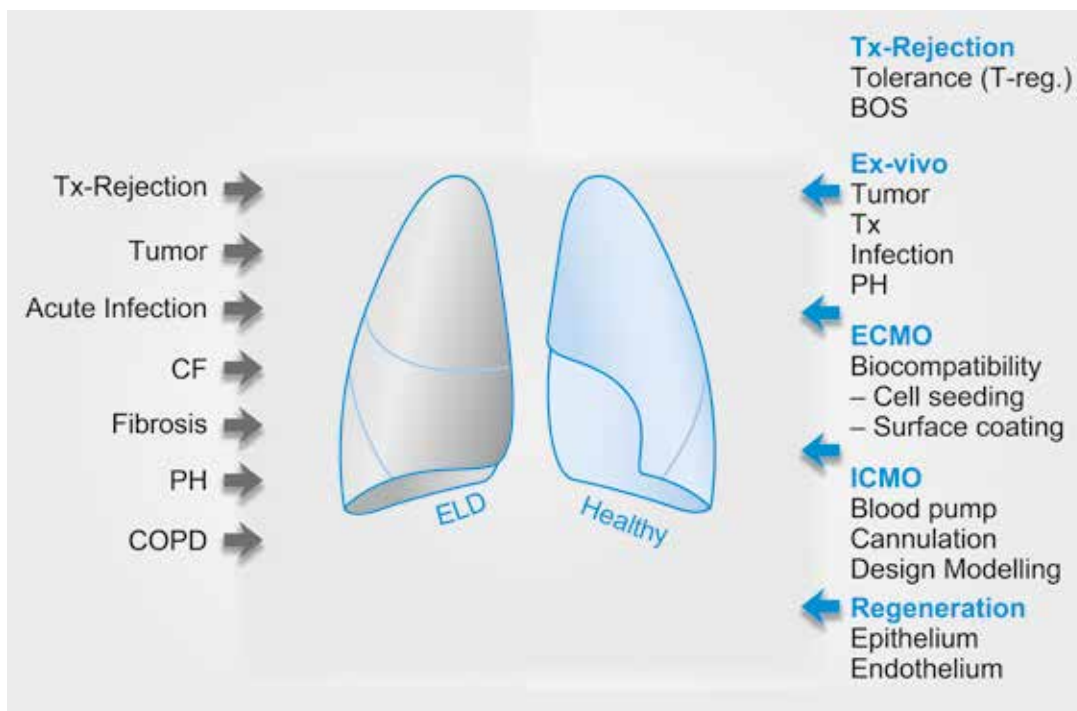
Dr. Annegret Zurawski (BREATH)

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 2016

Basic Science Flagship Project

- ▶ Generation of induced pluripotent stem cells from PAH patients with heterozygous BMPR2 mutations as tool to identify new gene correctors/potentiators and evaluation as a possible new therapeutic approach

Translational Flagship Project

- ▶ Establish bioengineered lung tissue for transplantation by using iPS-derived endothelial and epithelial cells on bioengineered lung lobes in rodents.

Clinical Flagship Project

- ▶ Tailored therapy to optimize immunosuppression guided by DNA virus monitoring after lung transplantation

Work Package 1: Transplantation

- ▶ Optimize transplantation results by *ex vivo* perfusion of donor lungs, avoiding acute rejection and developing strategies against chronic rejection.

Work Package 2

- ▶ Extracorporeal membrane oxygenation (ECMO): Improving the results of ECMO therapy by refining indication and developing innovative technologies using a new anti-inflammatory concept for better hemocompatibility and long-term applications

Work Package 3

- ▶ Regeneration: Regeneration of the diseased lung by endogenous regeneration and cell therapy towards tissue engineering of the entire organ
- ▶ Optimization of differentiation protocols for generation of epithelial cell types (airway epithelium) from human induced PSCs (hiPSCs).

Work Package 4

- ▶ *Ex vivo* lung perfusion (ELVP): Autotransplantation of the lung after *ex vivo* targeted therapy during ECMO support of the recipient employing the Organ Care System (OCS) in different models and for different diseases.

Work Package 5

- ▶ Intracorporeal membrane oxygenation (ICMO): Develop strategies and technologies from current ECMO concepts for improved blood pumps, oxygenators and cannulation techniques right through to an implantable device.

Work Package 6

- ▶ Health Care & Economics: Evaluation of costs and main cost drivers in Lung Transplantation and identification of factors improving reimbursement mechanisms.

Work Package 7

- ▶ Education: Enlarging the scope of a Postgraduate School of Extra-Corporeal Circulation for the training of health care personnel and physicians.

Research Highlight 2016

Biofunctionalisation strategies for the biohybrid lung

Patients with severe lung disease, such as Chronic Obstructive Pulmonary Disease (COPD), suffer from a disrupted gas-exchange function of the lungs, resulting in a reduced oxygen supply and increased carbon dioxide levels in the blood. The associated symptoms can be managed temporarily with medication, but lung transplantation remains the only currently available curative therapy option and is limited to a highly selected patient population. In cases of acute deterioration in the lung function or respiratory failure, patients can be supported by mechanical ventilation or via extracorporeal membrane oxygenation (ECMO), which temporarily ensures gas exchange and oxygenates the patient's blood. In the ECMO device, the gas exchange of the ECMO takes place in the artificial hollow fibres of the system, whereby the gas flows on the inside and the blood flows on the outside for gas transfer. This unavoidable and essential contact of the circulating blood with the artificial hollow fibres means that patients require anticoagulation medication to avoid the formation of blood clots, which can, however, increase the risk of bleeding complications.

Even with anticoagulation medication, deposits of blood components and blood clots can occur on the artificial surfaces several days after commencing ECMO, which decreases the blood flow through the narrow membrane mesh within the device, dramatically reducing the effective gas exchange. Working towards complete biocompatibility of the ECMO's artificial surfaces, recent research has focused on the physiological anti-thrombogenic properties of endothelial cells (EC), which line the inside of our vessels. EC have been used to colonize artificial materials in various applications, including work on the development of a biohybrid lung, which is hoped to offer patients a 'bridge to transplant' and ultimately also a 'final destination therapy' as an alternative to lung transplantation. With this goal in mind, the DZL "Bioartificial lung" group focuses on the biofunctionalisation of artificial surfaces for biomaterials, in particular the hollow-fibre membranes (HFM) of the ECMO device.



Fig. 1: Flow chamber setup for the exposure of endothelialised hollow fibre membranes to flow conditions.

In a recent study, published by Wiegmann et al. (2016), albumin/heparin-coated HFM were assessed in a bespoke flow chamber for the adhesion of EC and their resilience under the influence of different blood flow conditions. A seeding protocol was established to create a uniform distribution of EC on the HFM surface, which formed a viable, confluent EC monolayer following a cultivation phase under static conditions. The EC monolayer retained the endothelial phenotype throughout the duration of the experiment and the molecular biological assessment of the seeded EC indicated no change in the activity of genes responsible for the initiation of inflammation or coagulation. In addition, the EC monolayer proved to be resistant to blood flow-like conditions, without any change in the expression level of activation-relevant genes. The endothelium also maintained its physiological response to externally applied signalling molecules, such as $\text{TNF}\alpha$.

In addition to protein-, or peptide-containing surface coatings, the alternative method of titanium dioxide coating, de-

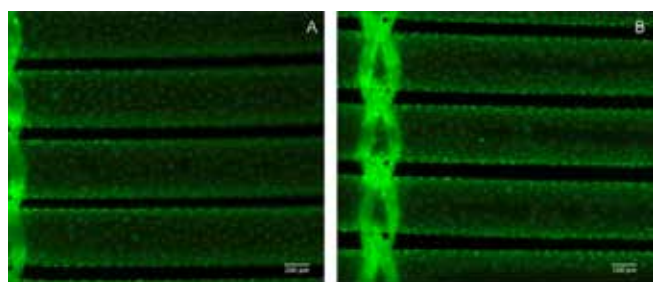


Fig. 2: Endothelial cells were seeded on hollow fibre membranes and stained with vital dye calcein (green). A) Viable EC were distributed uniformly throughout the HFM surface and formed a confluent monolayer. B) After exposure to flow conditions for 6 hours, EC remained adhered to the HFM surface.

posited on the gas exchange membrane using pulsed vacuum cathodic arc plasma deposition (PVCAPD) was investigated by Pflaum et al. (2017). The study demonstrated that Titanium Dioxide (TiO₂) could be successfully used to coat gas exchange membrane films and HFMs without any detectable damage to the membrane structure, while maintaining oxygen permeability. The TiO₂ layer successfully mediated the adhesion of EC, creating a vital and intact cell layer via cell-to-cell contacts (VE-Cadherin) which bound via focal adhesions to the collagen-IV matrix secreted by the EC. Moreover, the EC monolayer retained a non-inflammatory and non-thrombogenic state, was able to withstand physiological shear stresses and demonstrated a 'self-healing' capacity at areas of induced EC monolayer disruption (scratch assay).

These findings demonstrate the feasibility of creating endothelialised hollow fibre membranes, an essential step in the

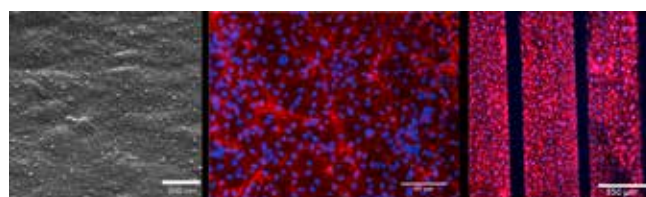


Fig 3.: Titanium dioxide-coated gas exchange membranes. A) SEM image of coated membrane reveals the uniform distribution of small TiO₂ particles. B) Immunofluorescence staining of TiO₂-coated membrane 14 days after seeding. EC (nuclei shown in blue) formed a confluent monolayer and were able to secrete a collagen-IV rich matrix (red) on the TiO₂ layer. C) The intercellular connection of EC within the monolayer, established on the HFM, was detected by immunofluorescence staining for VE-Cadherin (red).

development of biofunctionalized surfaces for a bioartificial lung.

Further information:

Wiegmann B, von Seggern H, Höffler K, Korossis S, Dipresa D, Pflaum M, Schmeckebier S, Seume J, Haverich A. Developing a biohybrid lung – sufficient endothelialization of poly-4-methyl-1-pentene gas exchange hollow-fibre membranes. *J Mech Behav Biomed Mater*. 2016 Jul;60:301-11. doi: 10.1016/j.jmbbm.2016.01.032.

Pflaum M, Kuhn-Kauffeldt M, Schmeckebier S, Dipresa D, Chauhan K, Wiegmann B, Haug RJ, Schein J, Haverich A, Korossis S. Endothelialization and characterization of titanium dioxide-coated gas-exchange membranes for application in the bioartificial lung. *Acta Biomater* 2016 10.1016/j.actbio.2016.12.017.

Lung Cancer

Scientific Coordinators of the Disease Area

Prof. Dr. Ursula Klingmüller (TLRC)

Prof. Dr. Michael Thomas (TLRC)

Administrative Coordinator of the Disease Area

Dr. Birgit Teucher (TLRC)

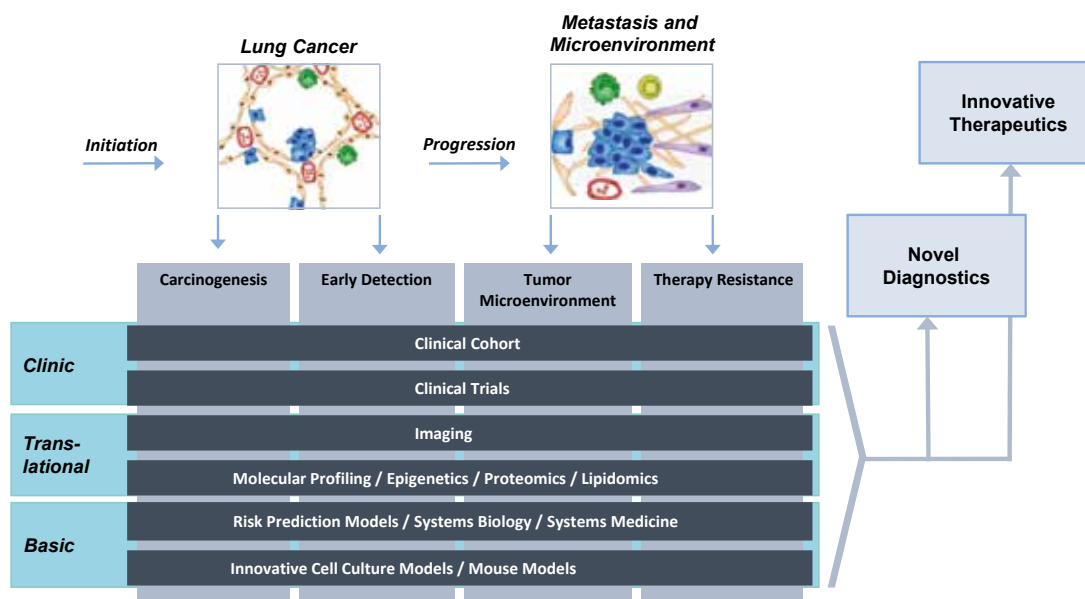
Participating DZL Partner Sites

All

Lung Cancer is one of the most common types of cancer in Germany and by far the leading cause of cancer deaths, often due to diagnosis at a late stage. Almost 40% of Non-Small Cell Lung Cancer (NSCLC) patients present with metastases at time of diagnosis. Advances in molecular profiling have led to new opportunities to develop targeted therapies that act on specific molecular targets of the cancer cell. Besides targeted therapy and chemotherapy immunotherapy has gained significance as the third main pillar of systemic therapy. Immune checkpoint inhibitors unmask the cancer cells and enhance the body's immune response against malignant cells. Today, in precision medicine multimodal therapy concepts enable application of the most effective treatment regimen for each patient.

However, not all patients respond to targeted therapy and immunotherapy. Thus, unraveling mechanisms of tumor progression is essential to identifying markers that predict clinical response. Therapeutic monitoring of these biomarkers allows early treatment adjustment. The capability to detect prognostic genetic material shed from tumors in blood samples may thus provide a real time low invasive assessment of tumor response to treatment. The potential of this 'liquid biopsy' approach is currently the subject of intense research.

Lung cancer research at the DZL is an interdisciplinary and integrative program. 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 of advancing biomarker-guided precision medicine.



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 2016

Basic Science Flagship Project

- ▶ Unravelling mechanisms that contribute to the deregulation of the TGF- β (transforming growth factor- β)- signaling pathway in lung cancer and its clinical significance for therapy resistance. Of particular interest for the deregulation of TGF-beta is the impact of the cell surface protein BAMBI (bone morphogenetic protein and activin membrane-bound inhibitor) as well as mutations in the EGFR (epidermal growth factor receptor) and p53 gene.

Translational Flagship Project

- ▶ Identification of molecular mechanisms that cause epigenetic deregulation in lung cancer and translation of these results into clinical use, in particular in early diagnostics and follow-up. Diagnostic panel of gene loci aberrantly methylated in lung cancer and appropriate assays will be developed and validated.

Clinical Flagship Project

- ▶ The aim is to prevent the inevitable occurrence of resistance to TKI-treatment of patients with the ALK+ driver mutation. In relevant patient cohorts the onset and mechanisms of resistance will be explored. Circulating tumor DNA (ctDNA) will be used to track molecular patterns of resistance and novel imaging protocols will be explored to capture early response to treatment. In Preclinical models the impact of chromosomal instability (CIN) on the occurrence of resistance will be assessed.

Work Package 1

- ▶ Elucidation of mechanisms that promote carcinogenesis and contribute to tumor evolution and therapy resistance. Experiments will employ advanced cell culture systems like 3D culture systems and pre-clinical mouse models for lung cancer and inflammation. Research activities will focus on the TGF-beta signaling pathway, the identification of mutated regulators of epigenetic pathways that contribute to tumor heterogeneity and mechanisms that promote chemotherapy resistance, in particular p53 mutations with oncogenic gain-of-functions and PI3/AKT signaling.

Work Package 2

- ▶ Utilization of patient cohorts and epidemiologic cohorts for molecular profiling to identify new biomarkers for risk stratification, early detection, therapy resistance and cancer progression (miRNA, ctDNA, Proteom). The new biomarkers will refine risk prediction models to improve the selection of high-risk subjects.

Work Package 3

- ▶ Investigation of the role of the tumor microenvironment for the development of targeted intervention strategies and individualization of treatment options. The employment of digital pathology will advance our knowledge of the composition of immune cells within the tumor and its changes during tumor progression. The communication between different cell types (fibroblasts, macrophages, lymphocytes) of the tumor microenvironment and their role in tumor progression will be investigated. Other activities are focused on the role of interleukins (IL-6, IL-22) and TGF-beta on immune cells in the microenvironment of the tumor to optimize treatments options with regard to checkpoint inhibitors, targeted natural killer cells and toll-like receptor (TLR-9).

Work Package 4

- ▶ The aim is an early detection of response and resistance to therapy as well as translation of new targets and procedures into proof-of-concept clinical trials to develop new treatment strategies for the improvement of long-term outcomes. The efficacy of therapies will be assessed by monitoring changes in circulating tumor DNA (ctDNA), molecular analysis of ctDNA and the employment of diffusion weighted magnetic resonance imaging (DWI-MRI) and perfusion analysis for the capture of early advents of response and resistance.

Research Highlight 2016

“BAMBI”– a potential new therapeutic target for non-small-cell lung cancer

Characteristic for non-small-cell lung cancer (NSCLC) is early metastatic disease and high mortality due to a lack of treatment options. Therefore, an important focus of the DZL research program is dedicated to the identification of new therapeutic targets whereby the TGF- β (transforming growth factor β) signaling pathway is a particularly promising candidate for intervention. TGF- β is a messenger protein that is involved in the regulation of many basic cellular functions and inflammation. In the context of tumorigenesis it is already known that TGF- β exerts a dual role in the development of lung cancer: during early stages of lung cancer the TGF- β signaling pathway inhibits the development of cancer cells by promoting cell death (apoptosis), while in late stages the TGF- β signaling pathway promotes invasion and metastasis of lung cancer cells.

In this study, scientists from the DZL sites ARCN and TLRC compared 133 NSCLC tissue samples from advanced lung cancer patients with 23 normal tissue samples and found various members of the TGF- β signaling pathway to be activated in NSCLC tissue, which in turn resulted in an increased metastatic potential of the cells. Further, it was noticed that the cell surface protein referred to as pseudo-receptor BAMBI (bone morphogenetic protein and activin membrane-bound inhibitor), was much less expressed in lung tumor tissue compared to normal tissue. If the level of expression of pseudo-receptor BAMBI was high, the activation of the TGF- β signaling cascade was reduced, which resulted in lower activation of gene expression and lower metastatic potential of the cells (Figure 1). It has been previously shown that the pseudo-receptor BAMBI forms a signaling incompetent complex with the functional TGF- β receptor. Thus, BAMBI is considered a negative regulator of the TGF- β signaling pathway. One explanation for the reduced production of BAMBI in lung cancer cells is the observation that the BAMBI gene promoter is more methylated in tumor cells – referred to as gene silencing – which results in less BAMBI on the cell surface. Thus, the silencing of the BAMBI gene is one mechanism by which the tumor promotes its growth.

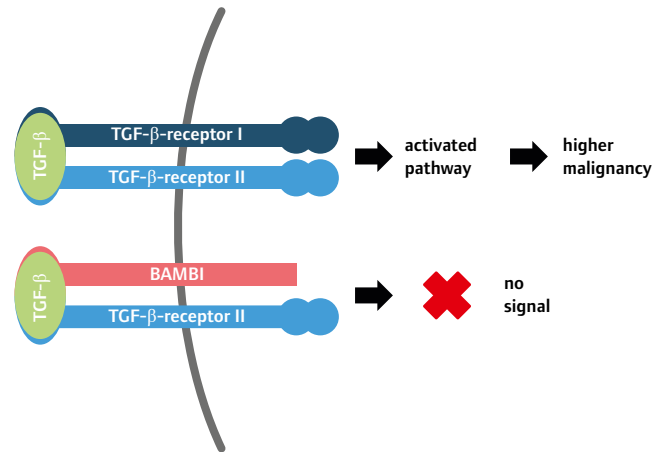


Figure 1: TGF- β (green) binds to the functional TGF- β receptor (upper panel) and thereby activates the TGF- β pathway. TGF- β is also able to bind to the BAMBI pseudoreceptor complex (lower panel). This doesn't lead to pathway activation and increased malignancy.

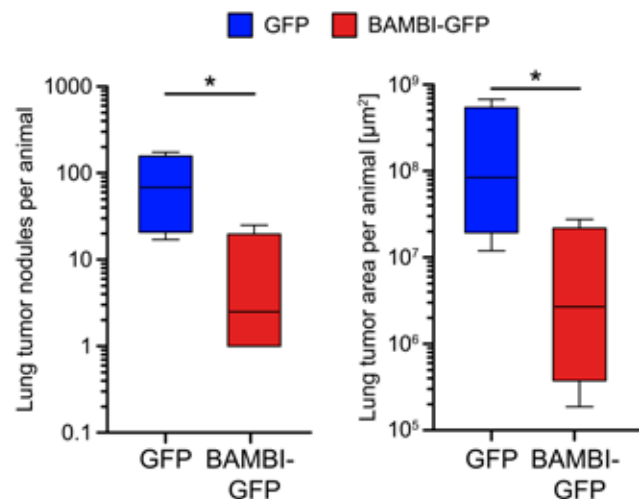


Figure 2: The tumor burden of mice injected with tumor cells in which BAMBI is reconstituted (red) is lower than in experiments with tumor cells without BAMBI reconstitution (blue). Shown are number of tumor nodules (left) and tumor area (right).

So, what happens if BAMBI is restored in tumor cells? Do these tumor cells lose their malignant potential? To address this question, a series of experiments focused on the effect of targeted reactivation of BAMBI expression and its effects by using retroviral vector technology. BAMBI expression was successfully up-regulated and the tumor cells were less invasive. Next, BAMBI reconstituted lung tumor cells were injected in mice. Although mice developed tumors, the group of mice that were injected with BAMBI reconstituted lung tumor cells developed fewer and smaller nodules, confirming that BAMBI reconstitution reduces TGF- β induced metastatic potential in vivo (Figure 2).

In summary, these results demonstrate that inhibition of the TGF- β signaling cascade may offer new opportunities for the treatment of non-small-cell lung cancer. The outcome of the study also underlines the importance of quantitative time-resolved investigations to unravel molecular mechanisms that contribute to cancer progression. The study was published in *Cancer Research* and is the result of a successful cooperation between basic scientists and clinicians at the DZL sites ARCN and TLRC.

Further Information:

Marwitz S, Depner S, Dvornikov D, Merkle R, Szczygieł M, Müller-Decker K, Lucarelli P, Wäsch M, Mairbörl H, Rabe KF, Kugler C, Vollmer E, Reck M, Scheufele S, Kröger M, Ammerpohl O, Siebert R, Goldmann T, Klingmüller U (2016) Downregulation of the TGFbeta Pseudoreceptor BAMBI in Non-Small Cell Lung Cancer Enhances TGFbeta Signaling and Invasion. *Cancer Res* 76: 3785-3801 (ARCN, TLRC)

Biobanking and Data Management Platform

Scientific Coordinators

Prof. Dr. Andreas Günther (UGMLC)

Dr. Thomas Muley (TLRC)

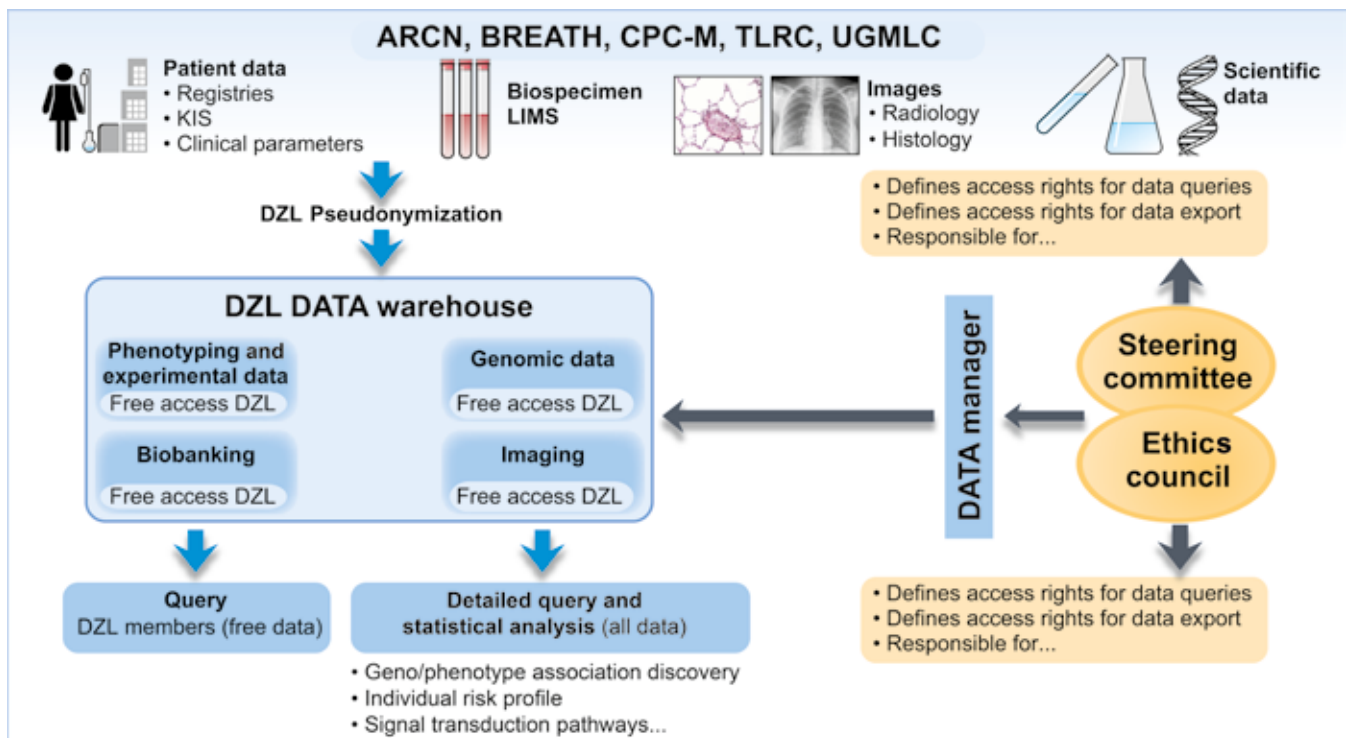
Administrative Coordinators

Dr. Jasmin Wagner (UGMLC)

Dr. Sylvia Weißmann (UGMLC)

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 Biobanking Platform 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 2016

Biobanking

- ▶ Full implementation of a centralized, automated, pseudonymized patient and biospecimen registry
- ▶ Prospective sampling of biospecimens from all types of pulmonary patient cohorts within the frame of a DZL-wide, harmonized informed consent procedure (e.g. approximately 1000 BAL (bronchoalveolar lavage), 5000 blood and 3000 lung tissue samples)
- ▶ Integration and long-term storage of biospecimens of existing studies/collections
- ▶ Development and implementation of consent management procedures
- ▶ Development of further standard operating procedures (SOPs) to cover all material acquisition and storage procedures
- ▶ Development/participation in DIN/ISO standard definition for biobanking
- ▶ Site specific teaching of scientists regarding specific biobanking issues
- ▶ Production of films, graphic materials and presentations for DZL educational purposes (internal website, optionally also open for general public)
- ▶ Cooperation in the TMF proposal: Development of data-interfaces for the use of the “Deutsches Biobankenregister” (German Biobank Registry) as a primary biospecimen catalog
- ▶ Further harmonization of operating procedures and policies concerning equipment and storage among all DZGs

Data Management

- ▶ Establishment of a DZL-wide, central data warehouse structure employing i2b2 as central software solution
- ▶ Complete annotation of all clinical parameters from different local registries with relevance to lung diseases
- ▶ Site specific teaching of scientists regarding the use of the DZL data warehouse (basic algorithm only)
- ▶ Data export on request and as specified within bylaws
- ▶ Data export to be used for Systems Medicine Analysis
- ▶ Development of web-based forms

Highlight of the Biobanking and Data Management Platform 2016

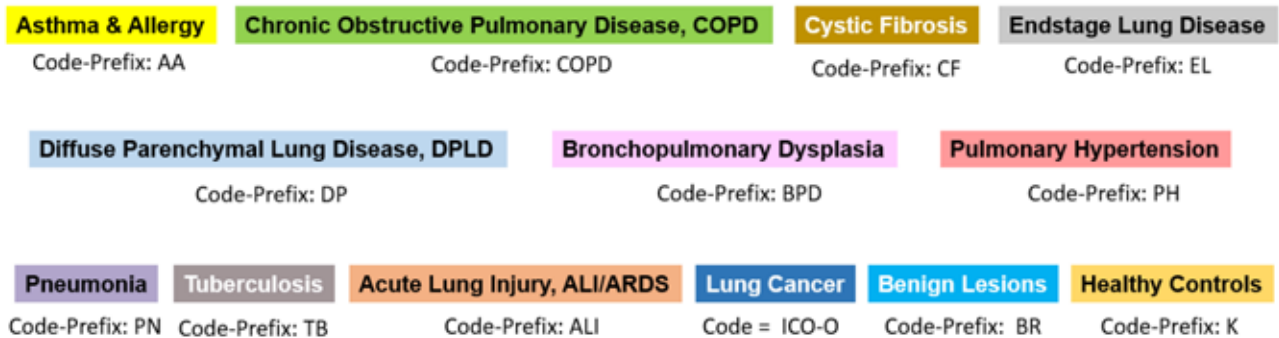
Development and implementation of a harmonized DZL phenotype and specimen classification system

For many pulmonary diseases, current clinical phenotyping or classification systems, such as the ICD-10-Code are only of limited use because they cannot depict individual symptoms. For this reason, the DZL Biobanking and Data Management Platform has developed its own classification system within the framework of the DZL's harmonization endeavours across its sites. This system is a prerequisite for the amalgamation and joint use of clinical data and information regarding bio-

materials throughout the DZL via the DZL data warehouse. In future, this system will make easy registration of biomaterials and targeted searches for biomaterials and clinical data possible through the DZL data warehouse.

In the list of phenotypes, the lung diseases will be divided into 13 main categories (disease classes), which will then be hierarchically further subclassified.

I. 13 Main Disease Categories:



II. Subcategorization:

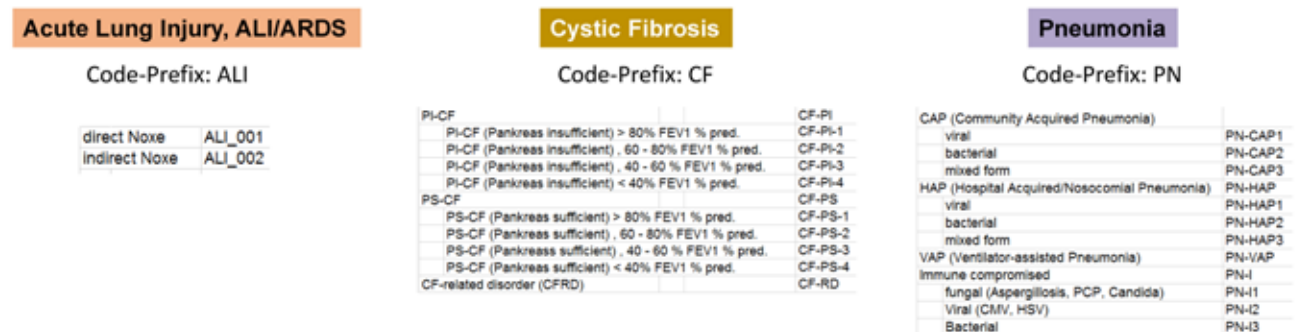


Fig. 1 List of phenotypes: 13 main categories (disease classes) and subclassification of Acute Lung Injury/ARDS, Cystic Fibrosis and Pneumonia as an example

I. 7 Main Categories:

Blood- Derivatives

Code-Prefix: PH

Swabs & Brushings

Code-Prefix: SB-

Lavage, Airway Aspirates, Sputum

Code-Prefix: LAS

Urine

Code-Prefix: U-

Tissue

Code-Prefix: T-

Cells

Code-Prefix: C-

Others

Code-Prefix: O-

II. Subclassification:

Blood- Derivatives

Code-Prefix: B-

| Blood products | Code | SPREC 2.0 |
|-------------------------|------|-----------|
| whole Blood | W | BLD |
| EDTA | WE | |
| Nucleic acid stabilized | WNA | |
| PAXgene | WNAP | PAX |
| Tempus Tube | WNAT | TEM |
| Streck Tube | WNAS | |
| Plasma | PL | PL1 |
| citratated | PLC | |
| heparinized | PLH | |
| EDTA | PLE | |
| Protease Inhibitor | PLPI | PIX |
| Serum | SE | SER |
| Gel | SEG | |
| Pellet | SEP | |

Swabs & Brushings

Code-Prefix: SB-

| Sampling types | Code | SPREC 2.0 |
|----------------|------|-----------|
| Swabs | SW | SWAB |
| Brushing | BRU | |
| | | |
| Localisation | Code | SPREC 2.0 |
| Bronchus | BRO | |
| Nose | NO | |
| Pharynx | PH | |
| Nasopharynx | NOPH | |
| Nasal Polyps | NOPO | |
| Rectum | REC | |
| Skin | SK | |
| | | |
| Stabil./Fix. | Code | SPREC 2.0 |
| native | FN | |
| Additiv | FA | ADD |
| Virom | FAV | |
| Microbiom | FAMI | |

| Examples | Code | SPREC 2.0 |
|---|--------|-----------|
| Blood and Derivates | | |
| EDTA whole Blood | B-WE | |
| whole Blood -RNA stabilized (Tempus tube) | B-WNAT | BLD-TEM |
| Plasma citratated | B-PLC | |
| Plasma heparinized | B-PLH | |
| Plasma EDTA | B-PLE | |
| Plasma Protease inhibitor (P100) stabilized | B-PLPI | PL1-PIX |
| Serum | B-SE | SER |

| Examples | Code |
|---------------------------|--------------|
| Swabs and Brushing | |
| Rectoanal Mucosal Swab | SB-SW-REC-N |
| Pharyngeal Swab | SB-SW-PH-N |
| Nasopharyngeal Swab | SB-SW-NOPH-N |
| Nasal Swab | SB-SW-NO-N |
| Nasal Brushing | SB-BRU-NO-N |
| Nasal Polyps | SB-NOPO |

Fig. 2: List of specimens: 7 main categories and subclassification and coding of blood samples, swabs/brushings as an example

Figure 1 shows the 13 main categories and the subclassification of Acute Lung Injury/ARDS, Cystic Fibrosis and Pneumonia as an example. Each phenotype is given a unique code (e.g. PN-CAP2 for bacterial, community-acquired pneumonia). In the list of specimens (Fig. 2), 7 main categories of

sample types are differentiated, which are then subdivided further according to method of acquisition, origin/localization and fixation/stabilization. The modular structure allows each sample type to be allotted an individual and unique code.

Imaging Platform

Scientific Coordinators

Prof. Dr. Heinz Fehrenbach (ARCN)

Prof. Dr. Hans-Ulrich Kauczor (TLRC)

Prof. Dr. Matthias Ochs (BREATH)

Administrative Coordinators

Dr. Birgit Teucher (TLRC)

Kerstin Burmester (TLRC)

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 2016, the first year of the second funding period, the Imaging Platform focused on the coordination and support of the activities in development and validation of Imaging Biomarkers as endpoints or surrogates in prospective clinical trials. In addition, a new project on the subject of "Growing and Ageing of Vessels and Airways (GAVA)" was initiated, which has the ambition to involve a broad skill base and bring together interdisciplinary approaches from across disease areas.

The following clinical trials supported by the Imaging Platform were continued or newly started in 2016:

1) Disease Area COPD: Functional Imaging in COPD – MR-COPD I (Cosyconet Subproject 7) and MR-COPD II – Imaging Disease Progression in COPD

2) Disease Area DPLD: Attention to Infants with Respiratory Risks (AIRR Studie) – the study aims at a better understanding of molecular mechanisms involved in bronchopulmonary dysplasia and advancement of early detection

3) Disease Area PH: Change-MRI (CTEPH DIAGNOSIS Europe – MRI) – a phase III diagnostic trial to demonstrate that functional lung MRI can replace VQ-SPECT in a diagnostic strategy for patients with suspected Chronic Thromboembolic Pulmonary Hypertension (CTEPH) where positive findings are veri-

fied with catheter pulmonary angiography (CPA), or computed tomography pulmonary angiography (CPA)

4) Disease Area LC: Early response capturing in the treatment of adenocarcinoma of the lung (ERT) – monitoring of early treatment response with diffusion weighted and dynamic CE-perfusion MR-imaging

5) Disease Area CF: Preventive Inhalation of Hypertonic Saline in Infants with Cystic Fibrosis (PRESIS) – a randomized, double-blind, controlled pilot study on the safety of hypertonic saline as preventive inhalation therapy in newborn patients with Cystic Fibrosis

Another important task of the Platform is the implementation of the Image Bank, a central database which will be linked to the data warehouse of the DZL. The use of this database complies 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.

One of the main themes of 2016 was data harmonization. Across-site harmonized procedures for data acquisition form the basis of a systematic, standardized, fully automatic quantification of image data. The Image eVALuation Service (IVA), developed at Heidelberg provides the technical requirements for high throughput evaluation of large amounts of image data. The results of the automatic image data analysis are available as reference values in the image database. A major milestone for data integration is the 2016 concept for secure data exchange between the DZL sites and the Image eVALuation Service. Communication is carried out using a software solution developed in Heidelberg, which simplifies data exchange for the sites while adhering to data protection regulations is provided.

Goals for 2016

Work Package 1

- ▶ Framework
 - › Continuous support from the central coordination office established in Heidelberg

Work Package 2

- ▶ Imaging Biomarkers
- ▶ Development, validation and implementation of imaging biomarkers in prospective DZL-trials. Definition of standardized imaging read-outs as endpoints or surrogates.

Work Package 3

- ▶ Image Bank
- ▶ Implementation of the image database. Integration of clinical trial data in accordance with German data protection regulations.

Work Package 4

- ▶ Image Evaluation
- ▶ Procurement and establishment of a system for the evaluation of image data.

Work Package 5

- ▶ Education
- ▶ Development of a concept for webinars or online-tutorials on how to use imaging and imaging biomarkers for across the sites training activities

Work Package 6

- ▶ Compile image-based results from projects on “Growing and ageing of airways and vessels (GAVA)”
- ▶ Identification of studies and projects related to GAVA. Review of imaging technology and imaging biomarkers used in GAVA-projects.

Research Highlight Microscopy 2016

Autofluorescence multiphoton microscopy for visualization of cellular dynamics in murine and human airways

Cells of the immune system are mobile and interact with many other cells in the tissue during airway inflammation. To understand the inflammatory process, it is necessary to follow inflammatory cells over time. Current approaches focus on genetically labeled cells in mice, but do not consider the surrounding tissue. The aim of this work in cooperation with scientists from Lübeck (ARCN) and Gießen (UGMLC) was to investigate if autofluorescence multiphoton microscopy is suitable to observe the movement of cells of the immune system over time, and at the same time to visualize the structure of the tissue.

Using this method, both the tissue structure (Figure 1) and the cells of the immune system could be imaged in living mice as well as in tissue preparations of humans and mice. This allowed us to detect an inflammation in living tissue (Figure 2). In addition, it was possible to track the movement of cells over time. With additional use of fluorescently labeled antibodies

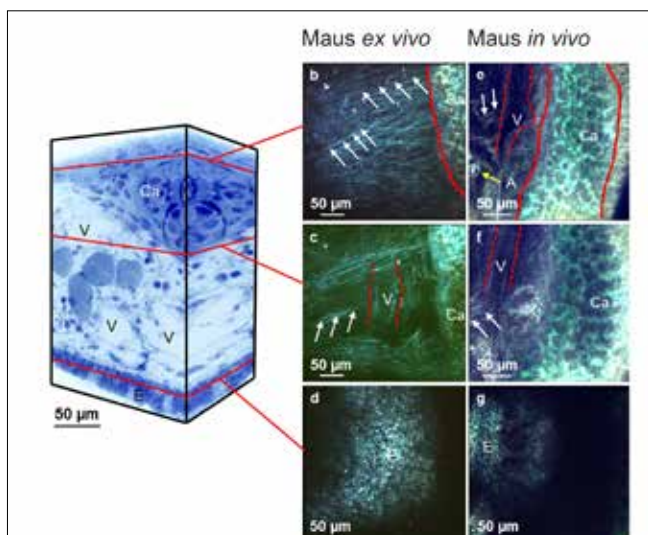


Figure 1: Comparison of conventional histological section and autofluorescence-multiphoton microscopy. Arrows: fibers, Ca: cartilage, V: vessel, A: adipocyte, E: epithelium.

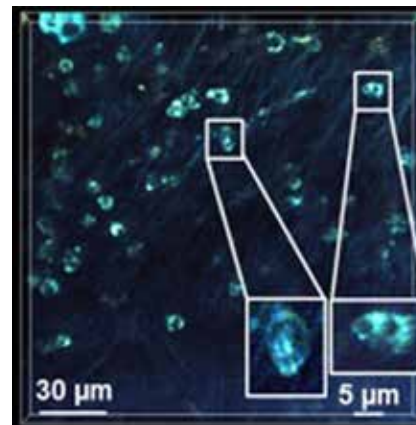


Figure 2: Detection of granulocytes during an allergic airway inflammation with autofluorescence microscopy.

it was possible to identify specific subtypes of cells of the immune system. With this approach we detected an unexpected interaction between neutrophilic and eosinophilic granulocytes and allergen-uptaking cells during an allergic immune reaction.

Since this approach is independent of genetically labeled cells, it can be used for human material. In the long term, it might be possible to integrate a multiphoton microscope into an endoscope to detect pathological processes in patients.

Further information:

Kretschmer S, Pieper M, Hüttmann G, Bölke T, Wollenberg B, Marsh LM, Garn H, König P. Autofluorescence multiphoton microscopy for visualization of tissue morphology and cellular dynamics in murine and human airways. *Lab Invest* 2016, 96: 918-931.

Research Highlight Radiology 2016

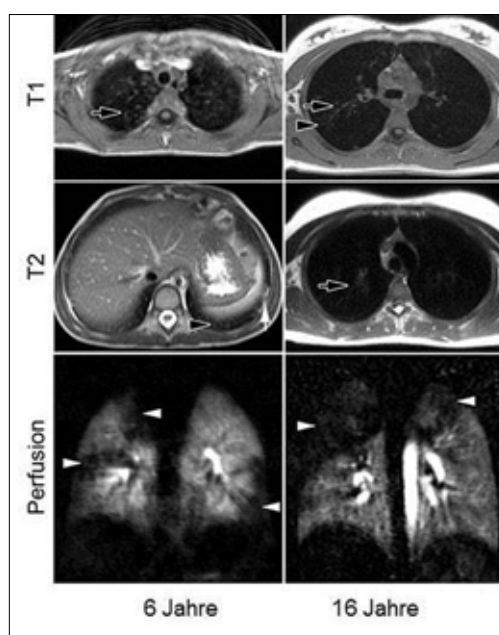
Non-invasive and radiation-free early diagnosis and therapeutic monitoring of patients with cystic fibrosis lung disease

Results published in the *American Journal of Respiratory and Critical Care Medicine* confirm the sensitivity of magnetic resonance imaging (MRI) and the lung clearance index (LCI), a measure of abnormal ventilation distribution, to detect damage to the lung in Cystic Fibrosis (CF) from early infancy.

This cross-sectional study was conducted at the Translational Lung Research Center Heidelberg (TLRC) in close collaboration with the Cystic Fibrosis Center at the Department of Pediatric and Adolescent Medicines, the Department of Diagnostic and Interventional Radiology, and the Department of Translational Pulmonology at Heidelberg University Hospital.

LCI determined by age-adapted multiple breath washout (MBW) techniques, and MRI studies were performed in 97 clinically stable children with CF across the pediatric age range (0.2–21.1 y). Furthermore, LCI (n=26) or MRI (n=10) were performed at the time of pulmonary exacerbation before and after antibiotic therapy. MRI was evaluated using a dedicated morpho-functional score.

In the majority of the examined children and adolescents, the detection of abnormalities in lung tissue or perfusion using MRI (Figure) reflected the need to breathe their entire lung volume more often than usual to fully clear their lungs from a marker gas (increased LCI).



Morpho-functional MRI depicts the regional distribution of typical findings in CF lung disease such as bronchiectasis (black arrow), mucus plugging (black arrowhead), pleural reaction (white arrow) as well as perfusion abnormalities (white arrowhead).

This is the first study that has examined the relationship between LCI and early abnormalities in lung structure and perfusion detected by MRI in children with CF. These data demonstrates that LCI correlates with the global extent of abnormalities, as well as structural airways disease detected by MRI, and that both techniques are sensitive to detect differences in disease severity and response to antibiotic therapy for pulmonary exacerbations in children with CF across the entire pediatric age range. In addition, MRI enables detection of regional disease heterogeneity, including regional mucus plugging that causes abnormal lung perfusion observed in early CF lung disease.

These results show that LCI and MRI may be useful as complementary sensitive and noninvasive outcome

measures for early detection and monitoring and as endpoints in early intervention trials in children with Cystic Fibrosis.

Further information:

Stahl M, Wielpütz MO, Graeber SY, Joachim C, Sommerburg O, Kauczor H-U, Puderbach M, Eichinger M, Mall MA. Comparison of lung clearance index and magnetic resonance imaging for assessment of lung disease in children with cystic fibrosis. *American Journal of Respiratory And Critical Care Medicine* 2016.

Clinical Trial Board and clinical studies in the DZL

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)

Administrative Coordinator

Dr. Annegret Zurawski (BREATH)

The DZL annually allocates a portion of its budget for innovative clinical trials based on the initiatives of DZL scientists (Investigator-Initiated Trials). These competitively awarded funds allow DZL investigators (DZL-PIs) 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. Since 2012, annual calls for proposals have been distributed to DZL-PIs, giving them the opportunity to apply for these funds. The proposals are then 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.

In the following Table, the clinical studies selected according to this procedure (Investigator-Initiated Trials) and currently running in this reporting year are listed.

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

In addition, in 2016, for the second time, DZL investigators were able to apply for special 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 from other sponsors, e.g. the DFG or the BMBF. In this reporting year, nine applications have been prepared with this financial support.



Investigator-Initiated Trials supported with DZL Funds

| Coordinating PIs | Disease Area | DZL Partner Site(s) Involved | Title |
|--|---|------------------------------|--|
| Behr J / Günther A | Diffuse Parenchymal Lung Disease (DPLD) | all | Exploratory efficacy and safety study of oral pirfenidone for progressive, non-IPF lung fibrosis (RELIEF in lung fibrosis) |
| Griese M | Diffuse Parenchymal Lung Disease (DPLD) | all | Hydroxychloroquine (HCQ) in pediatric ILD (= children's interstitial lung disease; chILD) |
| Herold S / Lohmeyer J / Welte T | Pneumonia and Acute Lung Injury | BREATH, UGMLC | Promotion of host defense and alveolar barrier regeneration by inhaled GM-CSF in patients with pneumonia-associated ARDS |
| Heußel C | Lung Cancer | BREATH, CPC-M, TLRC, UGMLC | Early response capturing in the treatment of adenocarcinoma |
| Jobst B | COPD | all | Imaging disease progression in COPD |
| Kauke T / Winter H | End-Stage Lung Disease | BREATH, CPC-M | Impact of de-novo donor-specific antibodies on short- and long-term survival following single and double lung transplantation |
| Kreuter M / Vogelmeier C / Herth F | COPD | TLRC, UGMLC | Exploring efficacy of periodontal treatment on systemic inflammation and for prevention of exacerbations in patients with COPD: A multi-center, prospective, randomized, controlled, parallel-group pilot study |
| Mall M | Cystic Fibrosis (Mucoviscidosis) | 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) |
| Seeger W / Ghofrani A / Gall H | Pulmonary Hypertension | BREATH, UGMLC | Influence of specific PAH medication on right ventricular function in patients with pulmonary arterial hypertension |
| Thomas M / Huber R | Lung Cancer | ARCN, CPC-M, TLRC | Comprehensive characterization of Non-Small Cell Lung Cancer (NSCLC) by integrated clinical and molecular analysis |
| Tümmler B | Cystic Fibrosis (Mucoviscidosis) | 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 J | 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. |
| Vogelmeier C | COPD | ARCN, BREATH, UGMLC | Clinical study to investigate safety, tolerability, efficacy, pharmacokinetics and pharmacodynamics of multiple doses of the human GATA-3-specific DNzyme solution SB010 in patients with moderate to severe COPD – A randomised, double-blind, parallel, multicentre, phase IIa pilot study |
| Voswinkel R / Vogelmeier C | COPD | ARCN, UGMLC | Clinical validation of the iNOS-EMAPII axis as biomarkers, predictors and novel targets in COPD |
| Zabel P / Herth F / König I / Rabe K / Welte T | COPD | ARCN, BREATH, TLRC | Evaluation of non-invasive pursed-lip breathing ventilation in advanced COPD |

DZL Technology Transfer Consortium

Chairmen

Dr. Christian Stein (MD, Ascenion GmbH)

Dr. Peter Stumpf (MD, TransMIT GmbH)

Administrative Coordinator

Dr. Annegret Zurawski (BREATH)

Scientific Adviser

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
- 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:



The DZL Technology Transfer Consortium screened all abstracts submitted for the 2016 Annual Meeting and identified several that had potential intellectual property considerations.

DZL Cooperations and Networks

In the German Center for Lung Research (DZL), more than 230 scientists and their work groups, currently from a total of 28 university and non-university research institutions as well as clinics at five sites in Germany, all work together. Thus there is an intensive exchange, between DZL researchers both 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 members of the DZL, including many 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 430 scientists and clinicians met on 1 and 2 February, 2016, at the 5th DZL Annual Meeting in Hannover, to enter, after successful reassessment, the second funding period of the Center. At the same time, it was the best attended meeting since the Kick-off Meeting in 2012 near Frankfurt/Main, reflecting the enormous growth of the DZL and the increasing importance of the consortium. At the Annual Meeting, representatives were welcomed from the COSYCONET (German COPD and Systemic Consequences–Comorbidities Network), that at the start of the new funding period is firmly anchored in the DZL as an Associated Partner. With presentations on the strategic concepts of the Disease Areas and the Platforms, talks on the highlights by young researchers from the various research areas as well as the presentation of around 230 individual papers in moderated poster sessions and poster tours, there were numerous opportunities for intensive scientific exchange and maintaining contacts. In an earlier screening, members of the DZL Technology Transfer Consortium were able to identify 20 abstracts with patent-relevant content amongst all those submitted.

The members of the Scientific Board attending the meeting strongly supported the Board of Directors with advice on the results of the review and planning for the second fund-

ing period. Already on the day before the start of the Annual Meeting, participants in the DZL Mentoring Program “Careers in Respiratory Medicine” were able to take part in an exciting workshop about principles, methods and exercises on the subject of “conversation”. Following this, they were joined by their mentors at a get-together to discuss their projects with them. On the second day, the numerous work groups were able to meet to discuss the current projects, the feedback from the reviewers and plans for the next funding period. Members of the Biobanking and Data Management Platform took advantage of the opportunity to see for themselves the Hannover Unified Biobank at the Clinical Research Center Hannover.

Lung researchers from all parts of the world met on 16 and 17 June, 2016 in Hamburg for the 5th DZL International Symposium. This year’s Symposium carried the motto “Networks in Lung Research”. Together with the German Centers for Cardiovascular Research (DZKH) and Infection Research (DZIF) and the Excellence Cluster “Inflammation at Interfaces”, the participants explored the bordering areas of their disciplines. Renowned international and national speakers gave presentations on the current status of their areas of expertise to about 150 doctors and scientists, whilst young researchers were also given the opportunity to present their own projects in the form of short talks or posters.

Furthermore, numerous other events involving the DZL have taken place at the Center’s partner sites.

The German Center for Lung Research has, since its founding, been part of several networks conducting research into various pulmonary diseases and is associated with other organizations that contribute to the realization of research projects. The expansion and development of 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 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 the clinic 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 such as patient fora on special subjects. Together with the DZL, in 2016 the Lung Information Service also organized patient fora at a number of DZL sites.

Thus the DZL, together with the LIS, on 4 June invited patients to Giessen to attend the 15th Patient Lung Forum. Top-class speakers informed patients and their relatives for half a day about the current status of knowledge about chronic lung diseases. With around 100 participants, the event at the University Clinic Giessen and Marburg was filled to capacity. After the event, the DZL and LIS sat down with representatives of the patient organizations for a round table discussion

about ways to make greater advances in the mutual concerns regarding the lung and how the interests of patients can become more deeply involved.

Since September 2016, the DZL and LIS also offer patients, their relatives and members of the general public who are interested an outline of the current clinical studies being carried out by DZL researchers. In the internet-based list on the LIS website, objectives, admission criteria, duration and investigation or treatment methods of each study are set out in layman's terms. Interested patients can then get directly into contact with the study center, thus gaining easier access to clinical studies. The list of studies will be regularly updated and expanded.

A particularly pleasant and important occurrence for the strengthening of representation of patient interests within the DZL was the successful appointment of Dr. Pippa Powell, Manager of the European Lung Foundation (ELF) to the Scientific Board of the DZL. ELF, as the founder of the European



5th DZL Annual Meeting in Hannover

Respiratory Society (ERS), aims to bring patients, the general public and pulmonary specialists together, to make a positive contribution to respiratory medicine.

Ever since the foundation of the DZL, there has been a close cooperation with the COSYCONET (German COPD and Systemic consequences – COMorbidities NETWORK) through scientists belonging to both institutions.

At the German-wide register for the pulmonary disease COPD, that is the fourth highest cause of death worldwide, 31 study centers are involved. 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 was 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 the 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 im-



portance 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) and, since the year end 2016/17, an associated partner of the DZL. Scientists at the DZL 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 has been connected with the National Cohort from the start through scientists from its own ranks and has in the meantime established an associated partnership. In this cooperation, projects on the prevalence of pulmonary health and diseases as well as other research projects are envisaged.

The longstanding cooperation of DZL researchers with PROGRESS (Pneumonia Research Network on Genetic Resistance and Susceptibility for the Evolution of Severe Sepsis) was formalized at the year end 2016/17 with the admission of the network as an associated partner. Research is being carried out on the genetic basis for disease pathogenesis and the resistance to community-acquired pneumonia. The main focus of the research is the question as to which factors influence whether pneumonia will take an uncomplicated or a difficult course – even up to a septic shock.

Since 2015, there has been an associated partnership with the Pulmonary Research Institute (PRI), based at the LungenClinic Grosshansdorf. 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 are 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 “Pneumologie”, the official journal of the DGP, the DZL and the DZK (Deutsches Zentralkomitee zur Bekämpfung der Tuberkulose). 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. For example, Member of the DZL Board, Prof. Dr. Klaus K. Rabe (Grosshansdorf/Kiel) is currently President of the DGP.

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 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 fields 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 rep-

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 was finalized in March 2017. 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 Tobacco (Aufklärung gegen Tabak e.V., AGT), that focuses on juve-

niles. Medical students from 30 faculties in Germany, Austria and Switzerland inform approximately 20,000 pupils from the 6th to 8th classes each year, on a voluntary basis, 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. As already in 2014, the campaign has again been acknowledged by the German Chancellor in 2017 in the competition “startsocial” as one of the seven most outstanding voluntary projects in Germany.

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, synergistic effects can thus 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





Patient forum Giessen, June 2016

Pulmonary Hypertension. A joint objective of the DZG is the continuous access to information from decision-makers and the broader public. The DZG centers were represented for the first time in April 2016 at the Annual Conference of the German Society of Internal Medicine (Deutsche Gesellschaft für Innere Medizin – DGIM) and held a workshop on “Data warehouse systems as a basis for personalized medicine” at the World Health Summit in October 2016. A particular highlight of the workshop was the talk by Professor Dr. Hans-Ulrich Prokosch, whom the DZL would like to welcome as a new member of the Scientific Advisory Board to strengthen the expertise in bioinformatics.

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 associa-

tion is marked, for example, by the appointment of Prof. Dr. Tobias Welte as Vice-President of the ERS in September 2016 or the chairing the ERS International Congress in Munich in 2014 by DZL scientists. 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 2016 in London. The ERS Congress is the largest meeting of respiratory researchers and clinicians in the world.

In 2016, the DZL has attended numerous other meetings and scientific conferences contributing presentations and scientific expertise, as for example at the first World Bronchiectasis Conference in July 2016 in Hannover and the 19th German Cystic Fibrosis Conference in November 2016 in Würzburg.

In addition, further numerous strategic partnerships of the individual DZL sites have been set up with international scientific and economic partners. Thus the expertise in industrial contacts could be strengthened by the acceptance of Prof. Dr. Stephen Rennard to become a member of the International Scientific Advisory Board of the DZL.

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.

Promotion of Junior Scientists and Equal Opportunities

Training the next generation of lung researchers is a top priority at the DZL. There are many different ways in which to support young researchers: graduate and youth development programs, such as special lung schools, a DZL mentoring program, positions as youth development leaders, grants in cooperation with other large lung institutions, poster sessions to present their own projects, workshops and awards, for example poster prizes at DZL events.

Youth development in site-specific programs

All DZL sites offer graduate training or youth development programs emphasizing lung research:

DZL Site Kiel, Lübeck, Grosshansdorf and Borstel (ARCN)

- Borstel Biomedical Research School (BBRS)
- Clinical Scientist Training at the University of Lübeck
- Graduate Centers at the Universities of Kiel and Lübeck
- Graduate programs from the DFG Excellence Initiative
- Junior Research Cluster “Chronoflammation – Circadian gated neutrophil inflammation” at the University of Lübeck

DZL Site Hannover (BREATH)

- Hannover Biomedical Research School (HBRS)
- HBRS Structured Medical Doctors’ Program (StrucMed Program)
- Ina Pichlmayer Mentoring-Program of Hannover Medical School for young female researchers studying for habilitation
- Lower Saxony International Summer Academy (LISA)
- BREATH quarterly DZL colloquia

DZL Site Munich (CPC-M)

- CPC Research School “Lung Biology and Disease”
- Doctoral studies „Molecular and clinical translational medicine” (FöFoLe) at the University Clinic Munich

- Else Kröner-Forschungskollegien „Rare Diseases of the Immune System” and „Immunotherapy in the Treatment of Cancer”
- European Respiratory Society (ERS) Summer School
- European network for translational research in children’s and adult interstitial lung disease (CA COST Action CA16125)
- Helmholtz Graduate School Environmental Health (HELENA)
- Helmholtz Mentoring Program „Taking the Lead”
- International Doctoral Student Program „i-Target: Immunotargeting of Cancer”
- Life Science Campus Network Munich
- Master of Business Research (PhD Program), Munich School of Management at the Ludwig-Maximilians-Universität München (LMU)
- Munich Medical Research School (MMRS)
- Oncology Winter School of the LMU
- Training network IMMUTRAIN (HORIZON 2020 ITN)

DZL Site Heidelberg (TLRC)

- Hartmut Hoffmann-Berling International Graduate School of Molecular and Cellular Biology (HBIGS)
- Research projects in TLRC laboratories
- Monthly TLRC research seminars

DZL Site Giessen, Marburg, Bad Nauheim (UGMLC)

- International Max Planck Research School for Heart and Lung Research (IMPRS-HLR)
- Molecular Biology and Medicine of the Lung Program (MB-ML-Program)
- UGMLC School

DZL Mentoring Program

The DZL mentoring program “Careers in Respiratory Medicine” supports highly motivated young scientists and clinicians in the field of lung biology and respiratory medicine in the planning of their career, to help them qualify for leading positions. The program was initiated in 2014 and started officially in early 2015 at the DZL Annual Meeting in Hamburg. 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 DZL Annual Meeting in early 2016 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. Due to the success of the program, a new round of applications was started at the end of 2016.

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.

Equal Opportunities

Measures to ensure equal opportunities are carried out in close cooperation with the appropriate institutions at DZL partner sites. In the context of the gender equality programs of the participating university partners, 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, the percentage of female Principal Investigators (PIs) has increased from 14 % in 2011 to 23 % in 2016, when the percentage of female personnel funded by the DZL had reached 68 %.

The Public Face of the DZL

Informing the general public, decision-makers, patients and other target groups about pulmonary diseases and lung health is very important to the DZL. Despite increasing morbidity rates, there still tends to be insufficient awareness of pulmonary diseases compared to other widespread diseases.

The DZL is 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, through its internet presence (www.dzl.de).



de), a Newsletter and through joint activities with the Lungeninformationsdienst (German Lung Information Service), for instance events organized for patients. At the end of 2016, planning had also started for activities celebrating the 5th Anniversary of the DZL.

Several times a year, as again in 2016, the DZL also publishes the latest research results, event information, new appointments and other news about the Center on its Notices pages in the scientific journal „Pneumologie“.

With numerous news items about DZL lung research and a great deal of information on the background and structure of the DZL, the range of information offered again in 2016 could be expanded further on the DZL internet site. The special homepage section „New this week in PubMed“ shows the latest publications by DZL researchers on a weekly basis.

The research association also introduces itself in a short film portrait that can be found on the homepage as well as on YouTube.

In 2016, the comprehensive DZL Annual Report 2015 was published again in both English and German. Alongside the achievements and highlights of the year 2015, the report presents the numerous successes of the DZL since its foundation. Furthermore, diverse publications by and with DZL researchers have been released in specialist magazines and press articles.

The DZL, together with the other German Centers for Health Research (DZG), organizes events such as an annual session at the World Health Summit, to make various target groups aware of its concerns and its activities.

DZL at Conventions

In 2016, the DZL was represented at many large conventions. With an information stand, numerous award winners and presentations by its own scientists, the DZL played a highly visible role at the 57th Congress of the German Respiratory Society (Deutsche Gesellschaft für Pneumologie und Beatmungs-



The ERS (Past-) President Prof. Dr. J. Vestbo (2nd left) and Prof. Dr. G. Joos (left) at the DZL booth with Dr. A. Zurawski (DZL) and S. Baumgarten (DZL) at the ERS Congress 2016 in London

medizin e. V., DGP). The DGP Congress, held this time in Leipzig, under the motto “Innovative Pneumology”, represents the largest scientific forum in the field of respiratory medicine in the German-speaking world. In his Opening Speech, the former DGP President, Dr. Berthold Jany acknowledged the basic research and translational research carried out by the DZL as an immense gain for respiratory medicine.

On a national level, the DZL was also represented for the first time together with the DZG at the Annual Conference of the German Society of Internal Medicine (Deutsche Gesellschaft für Innere Medizin, DGIM) in April 2016. At this congress, the DZL also took on the sponsorship of a symposium on the subject of “Individualized therapy of obstructive airway diseases”.

At the ERS (European Respiratory Society) International Congress in London in September 2016, the DZL was also present with award winners, speakers and session chairs. In the Congress Area “World Village”, together with other professional associations from all over the world, the DZL provided information about its activities and welcomed the ERS (Past-) Presidents, Prof. Dr. Jørgen Vestbo and Prof. Dr. Guy Joos to its booth. The DZL’s presence at the largest congress in the world on respiratory medicine, with more than 22,600 people from more than 120 countries worldwide contributes vastly towards making the DZL more visible, both nationally and internationally.

In 2016, the DZL was also involved in numerous meetings and specialist congresses, contributing with contributions and scientific expertise, as for example at the First World Bronchiectasis Conference in July 2016 in Hannover and at the 19th Cystic Fibrosis Meeting in November 2016 in Würzburg.



5th International DZL Symposium in June 2016 in Hamburg

DZL Meetings for the Scientific Community

Even in these times of modern media, personal exchange between scientists at the numerous DZL partner institutes from various sites in Germany are essential. The most important and largest meeting is the DZL Annual Meeting, which takes place at each of the Center’s sites in turn. On 1 and 2 February 2016, more than 430 scientists, clinicians and young researchers discussed their project results, their strategies and research aims at the 5th Annual Meeting in Hannover. The work groups of the Disease Areas and Platforms take advantage of this opportunity for the mutual exchange information and ideas and for intensive consultation.

In order to carry out research on pulmonary diseases and treat them more effectively, it is essential to also exchange information beyond the national borders and the annual interna-



5th DZL Annual Conference in February 2016 in Hannover

tional DZL symposium contributes to this. The 5th International DZL Symposium in June 2016 in Hamburg brought together about 150 top-class researchers and clinicians from around the world. Under the motto “Networks in Lung Research”, the conference applied itself, among other things, to epidemiology, which concerns not only the areas of cardiology and infectiology, but also pneumology. Initially organized in cooperation with the German Center for Cardiovascular Research (Deutsches Zentrum für Herz-Kreislauf-Forschung, DZHK) and the German Center for Infection Research (Deutsches Zentrum für Infektionsforschung, DZHK) as well as the Excellence Cluster „Inflammation at Interfaces“, the border areas of the disciplines were explored.

In addition, in 2015 numerous other national and international scientific events took place under the chairmanship of the DZL and DZL involvement at the Research Network sites.

Working together for Health Research – DZG Events

Besides their joint presence already mentioned at the Annual Meeting of the German Society of Internal Medicine (DGIM) in April 2016, the German Centers for Health Research also attended the World Health Summit in October 2016. Under this year’s chairmanship of the DZL, they jointly organized a workshop entitled „Data warehouse systems as a basis for personalized medicine“. Prof. Dr. Roland Eils, Project Leader at the DZL and in the German Consortium for Translational Cancer Research (DKTK), presented the current status of the data warehouse systems at the DZG. The Head of the Division of Theoretical Bioinformatics at the German Cancer Research Center (DKFZ) spoke about the challenges to be met on the way to a potential joint data warehouse system for the whole DZG. In a round of discussions, the participants worked out how, through joint initiatives, important advances can be achieved in the field of personalized medicine.

Focusing on Patients

Strategically, in its second funding period, the DZL is moving the concerns and interests of the patients more and more into focus. Ever since the DZL was founded, the Lung Information

Service (LIS) has been a professional and reliable partner for direct and understandable information for patients. During the year, the DZL and the LIS have organized six fora specially for patients and their relatives at the DZL sites, each with more than 100 attendees:

- 16 January 2016 (Hannover): Patient seminar “Pulmonary fibrosis”
- 27 February 2016 (Heidelberg): Symposium by the Cystic Fibrosis Center Heidelberg for patients and relatives
- 12 March 2016 (Hannover): Lung Forum „Bronchiectasis“
- 04 June 2016 (Giessen): Lung Forum „Chronic Lung Diseases – Treatment, Research, Healing“
- 06 October 2016 (Heidelberg): Patient Day on the subject of “Help with interstitial and rare pulmonary diseases”
- 07 December 2016 (Munich): Lung Forum „Chronic lung disease – what can I do?“

Another important part of the established contact with patients (or representatives) are the DZL round table discussions held since 2016, which allow a direct exchange on common concerns in the field of lung research. To strengthen the representation of patient interests in the DZL, Dr. Pippa Powell, Manager of the European Lung Foundation (ELF) was appointed to the Scientific Advisory Board of the DZL. Since the foundation of the European Respiratory Society (ERS), ELF has pursued the target of bringing together patients, the general public and those working in this specialist field, in order to make a positive contribution to respiratory medicine.

Since September 2016, the DZL and LIS also offer an online overview of the current clinical studies being carried out by DZL researchers. In the internet-based list on the LIS website (see below), objectives, admission criteria, duration and



Patient forum in Giessen in June 2016

investigation or treatment methods of each study are set out in layman's terms. Interested patients can then get directly into contact with the study center, thus gaining easier access to clinical studies. The list of studies will be regularly updated and expanded.

Lung Information Service

The Lung Information Service (LIS), based at the Helmholtz Center in Munich is an important part of the DZL. On its online portal: www.lungeninformationsdienst.de new research results and patient information are given that are easily understandable for the general public.



Key topics on the online portal of the Lung Information Service 2016:

- Lung and Breathing (January)
- Differences between Asthma and COPD (February)
- Lung Volume Reduction (March)
- Lung Transplantation (April)
- Bronchiectasis (May)
- Pulmonary Fibrosis (June)
- E-Cigarettes (July)
- Diagnosis of Lung Diseases (August)
- Sarcoidosis (September)
- Airway Infections (October)
- Movement and Sport (November)
- Clinical Studies (December)

The main basis for this news are the publications on patient-relevant topics in well-known specialist journals, of which a growing proportion have DZL members amongst the authors. There is also a great deal of interest in interviews and videos of the patient fora – amongst them with Prof. Dr. Jürgen Behr, Prof. Dr. Werner Seeger, Prof. Dr. Andreas Günther, Dr. Stefan Kuhnert and Prof. Dr. Jürgen Lohmeyer. Apart from the purely scientific content, in the online portal patients will also find the latest information about patient-relevant events, recommendations about newly published patient literature and announcements about interesting TV and radio programs.

From 2011 to 2016, the Lung Information Service has published more than 600 news articles on its homepage. In ad-



The Lung Information Service at the Lung Symposium in Hattingen

dition, the LIS offers a monthly newsletter. The already mentioned series of events "Patient Lung Forum", which covers a wide range of different lung diseases, is yet another important part of the Lung Information Service. The LIS also participated at other events with an information booth – at the Lung Symposium in Hattingen and the Transplantation Day in Munich. In addition, LIS and DZL organized a round table with representatives from patient organizations, so that they could be directly involved and receive feedback.

Since 2016, the Lung Information Service has been active on social media. It has its own Facebook profile and publishes new research information several times each week via Twitter. An average of 400 visitors per month download news from the News App for mobile devices also developed in 2016.

Highlights of the Year 2016

JANUARY

New Partner: COSYCONET

COSYCONET (German COPD and Systemic Consequences Comorbidities Network), a German-wide register for the lung disease COPD becomes an associated partner in the DZL.

Smoking obstructs the immune system

DZL scientists showed for the first time that cigarette smoke critically obstructs the safety mechanism of the immune system and lungs from COPD patients exhibit lower amounts of immunoproteases. The potential use as a biomarker is being examined.

FEBRUARY

5th DZL Annual Meeting in Hannover

Over 430 scientists, clinicians, young researchers and employees from the DZL sites met in Hannover on 1 and 2 February 2016 at the 5th internal Annual Meeting of the German Center for Lung Research and, after a successful reappraisal, celebrated together the start of the second funding period of the Center.



MARCH

Numerous research awards for DZL scientists at the DGP Congress

With numerous award winners, scientific presentations, an information booth

and a contribution to the DGP press conference, the DZL was present at the 57th Congress of the German Society for Pneumology and Respiratory Medicine (DGP) in March 2016 in Leipzig. DGB President Prof. Dr. Berthold Jany praised the research achievements of the DZL.



APRIL

DZL and DZG together at the Internal Medicine Congress

In April 2016, The DZL and DZG joined forces for the first time with an information booth and presentations at the Annual Meeting of the German Society for Internal Medicine (DGIM) in Mannheim.

DZL Researcher appointed to the German Ethics Committee

The DZL scientist, Prof. Dr. Ursula Klingmüller, was appointed to the German Ethics Committee by the President of the German Bundestag.



MAY

New target molecule discovered for the therapy of Non-Small Cell Lung Cancer

DZL scientists found that blocking the TGF- β signal pathway by increased production of the recently discovered protein BAMBI, presents a new option for the treatment of Non-Small Cell Lung Cancer.

JUNE

International DZL Symposium in Hamburg

Lung researchers from all over the world met at the 5th International DZL Symposium „Networks in Lung Research“ on 16 and 17 June in Hamburg to discuss together with representatives from the DZHK, the DZIF and the Excellence Cluster “Inflammation at Interfaces” selected aspects from basic, translational and clinical research.



Patients in the focus of the DZL

The DZL and the Lung Information Service hosted the 15th Patient Lung Forum in Giessen. Afterwards, they both exchanged views with patient organizations during a round table discussion on how joint concerns in the field of the lung can be addressed and patient interests become more involved.

JULY

Mechanism deciphered: protection against asthma and allergies

DZL scientists found that bacterial RNA can make a crucial contribution to protection against allergies and asthma. They are carrying out research to develop prevention and treatment approaches for both diseases.

First World Bronchiectasis Conference

In July 2016 representatives of the DZL and the German Bronchiectasis Register PROGNOSES organized the 1st World Bronchiectasis Conference in Hannover.

AUGUST

Progress in the treatment of Cystic Fibrosis

DZL researchers discovered in an initial systematic comparison that early lung changes in children with Cystic Fibrosis can be revealed almost as accurately and reliably by measuring the lung clearance index as by magnetic resonance imaging (MRI) – both are radiation-free methods.



SEPTEMBER

DZL at the world's largest lung congress in London

The DZL was again present at the International Congress of the European Respiratory Society (ERS) with its own information booth and presentations. The DZL scientist, Dr. Soni Savai-Pullamsetti, received an outstanding award for young researchers and the DZL Board Member, Prof. Dr. Tobias Welte, was elected Vice-President of the ERS during the conference.



CF newborn screening started throughout Germany

The newborn screening for Cystic Fibrosis, in which the DZL was involved in the preparation, was introduced throughout Germany.

Study platform started

An overview for patients and other interested parties of the current DZL clinical studies was started online.

OCTOBER

DZG at the World Health Summit in Berlin

The German Centers for Health Research organized a panel discussion on the subject of „Data warehouse sys-

tems as a basis for personalized medicine“ at the World Health Summit and determined, with international representatives, how significant progress can be made in the field of personalized medicine through joint initiatives.

Improved therapeutic possibility in advanced Lung Cancer

A clinical study with first authorship from the DZL showed that immunotherapy with the antibody Pembrolizumab can significantly improve the therapeutic options for patients with metastasized Non-Small Cell Lung Cancer.

NOVEMBER

Anniversary: 5 years DZL

In November 2011, the DZL was founded as an association. The DZL started its series of activities to celebrate its anniversary year.



Allergic asthma: fundamental disease mechanism found

DZL scientists have discovered in an animal model a fundamental disease mechanism in bronchial asthma and a possible new treatment strategy.

DECEMBER

New mechanism discovered in COPD

DZL scientists showed that, in a COPD, the molecule Wnt5a is increasingly produced, which is responsible for the structures of the lung no longer being able to heal.

Selected Prizes and Awards

| Award Winner | Award |
|--|--|
| Dr. Thomas Bahmer Grosshansdorf (Junior researcher) | Research Award of the Patienten-Selbsthilfeorganisation Lungenfibrose e. V. (patient self-help organization for pulmonary fibrosis) |
| Dr. Sabine Bartel Munich, Borstel (Junior researcher) | Doctoral Student Award of the Deutsche Lungenstiftung e. V. (German Lung Foundation) for outstanding work in the field of experimental research |
| Nicola Benjamin Heidelberg (Junior researcher) | Research Prize of the René Baumgart Foundation for Pulmonary Hypertension (shared prize) |
| PD Dr. Anna-Maria Dittrich Hannover | Johannes Wenner Research Award of the German Lung Foundation and the Society for Pediatric Pneumology |
| Prof. Dr. Birgit Ertl-Wagner Munich | Marie Curie Ring of the German Radiological Society (Deutsche Röntgengesellschaft e. V.) |
| Dr. Ilona Elisabeth Kammerl Munich (Junior researcher) | German Society for Pneumology and Respiratory Medicine (DGP) Research Award 2016 for outstanding work in the field of basic research |
| Prof. Dr. Ursula Klingmüller Heidelberg | Appointment to the German Ethics Board |
| Dr. Nikolaus Kneidinger /Dr. Teresa Kauke Munich | Georg Heberer Award 2016 of the Ludwig-Maximilians-Universität Munich (shared prize) |
| Dr. Rajkumar Savai Bad Nauheim/Gießen | Dr. Herbert Stolzenberg Award of the Justus Liebig University Giessen |
| Dr. Soni Savai-Pullamsetti Bad Nauheim/Gießen | Romain Pauwels Research Award of the European Respiratory Society |
| PD Dr. Olaf Sommerburg Heidelberg | Adolf Windorfer Award of the Mukoviszidose e. V. (German Cystic Fibrosis Association) for outstanding work in the field of research and therapy in cystic fibrosis |
| Dr. Benjamin Waschki Grosshansdorf (Junior researcher) | German Society for Pneumology and Respiratory Medicine (DGP) Research Award 2016 for outstanding work in the field of clinical research |
| Prof. Dr. Tobias Welte Hannover | Elected Vice President of the European Respiratory Society (ERS) |

The German Centers for Health Research

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

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 allows 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.

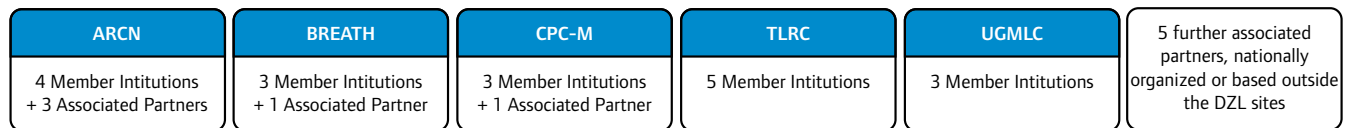
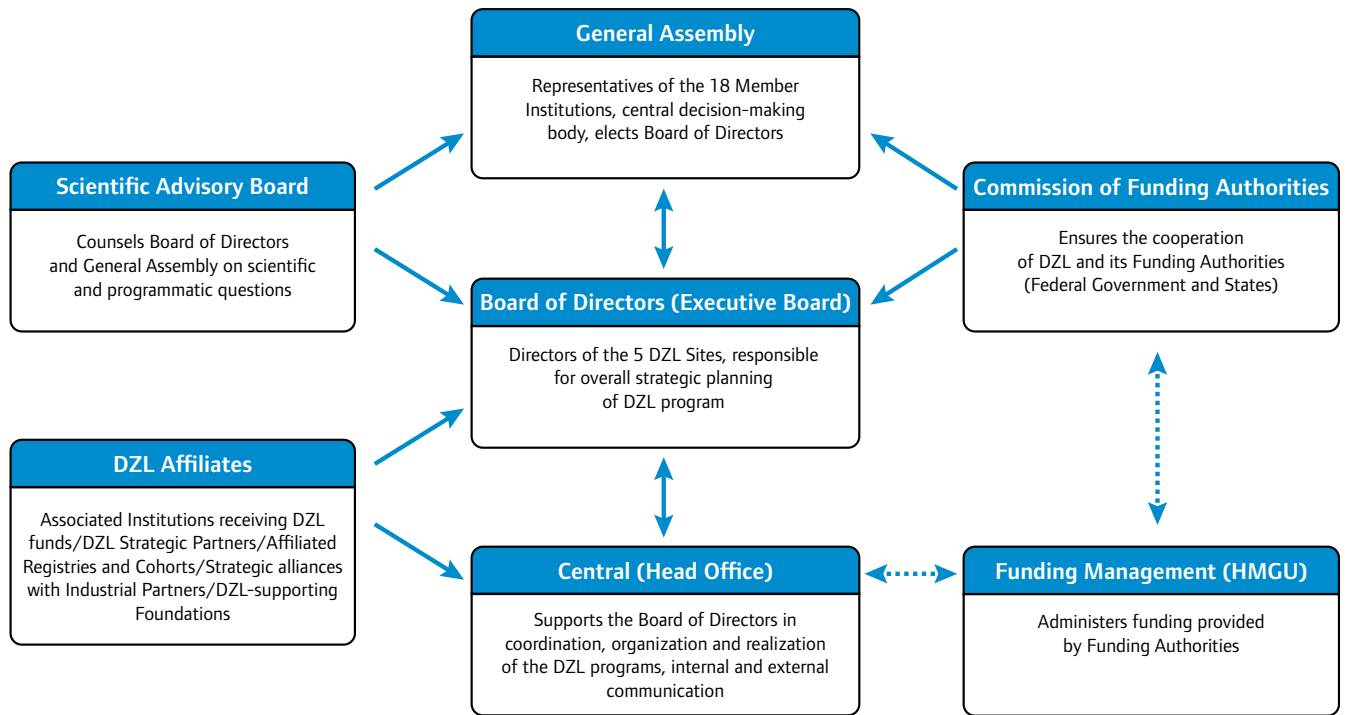
In 2009, the German Center for Neurodegenerative Diseases (DZNE) and the German Center for Diabetes Research (DZD) were founded. In 2011, four additional German Centers for Health Research were established: the German Center for Infection Research (DZIF), the German Center for Cardiovascular Research (DZHK), the German Consortium for Translational Cancer Research (DKTK) and the German Center for Lung Research (DZL).

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.



DZG Speakers and representatives at a Parliamentary Evening in Berlin.

DZL Organization



DZL Executive Board

- Prof. Dr. Werner Seeger (DZL Chairman and Speaker) – Director of the DZL Site Giessen, Marburg, Bad Nauheim (UGMLC)
- Prof. Dr. Marcus A. Mall – Director of the DZL Site Heidelberg (TLRC)
- Prof. Dr. Erika von Mutius – Director of the DZL Site Munich (CPC-M)
- 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)

DZL Head Office

- Dr. Christian Kalberlah, Managing Director
- Sabine Baumgarten, M. A., Press and Public Relations
- Susanne Klasen, Management Assistant

Scientific Advisory Board

The Scientific Advisory Board of the DZL is made up of internationally acclaimed experts in lung research. The twelve members of the Scientific Advisory Board are:

Jacob I. Sznajder

Chairman of the Scientific Advisory Board
Chief, Division of Medicine-Pulmonary, Ernest S. Bazley
Professor of Asthma and Related Disorders, Northwestern
University Feinberg School of Medicine; USA

Peter J. Barnes

Head of Respiratory Medicine, Imperial College London; UK

Rachel Chambers

Professor of Respiratory Cell and Molecular Biology, Center
for Respiratory Research, University College London; UK

Jeffrey M. Drazen

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

Stuart Elborn

Professor of Respiratory Medicine, Director Cystic Fibrosis
Center, Belfast City Hospital, President of the European
Cystic Fibrosis Society ECFS, Centre for Infection and Immunity,
Queen's University Belfast; Northern Ireland

Mark Gladwin

Division Chief, Pulmonary, Allergy, and Critical Care
Medicine, Director Vascular Medicine Institute, University of
Pittsburgh Medical Center; USA

Pippa Powell

Director of the European Lung Foundation (ELF), Sheffield;
UK

Hans-Ulrich Prokosch

Holder of the Chair for Medical Informatics, Friedrich-
Alexander-Universität Erlangen-Nürnberg; Chief Information
Officer, Universitätsklinikum Erlangen; former Member of the
Board of the German Society for Medical Informatics, Biometry
and Epidemiology (GMDS); D

Marlene Rabinovitch

Professor of Pediatric Cardiology, Stanford University School
of Medicine; USA

Stephen Rennard

Larson Professor of Medicine in the Pulmonary and Critical
Care Medicine Section, and courtesy professor of the
Department of Pathology and Microbiology and the Department
of Genetics, Cell Biology and Anatomy, University of
Nebraska, AstraZeneca; USA

Susan Shurin

Deputy Director, National Heart, Lung and Blood Institute
(NHLBI), National Institutes of Health (NIH); USA

Peter M. Suter

Akademien der Wissenschaften Schweiz, Centre Médical Uni-
versitaire, University of Geneva; CH

Head of Funding Management

- Dr. Dorothe Burggraf – Finance Department (Commercial
Funding Management, Helmholtz Zentrum München)

General Assembly

Currently, 18 member institutions belong to the DZL. In
addition, the DZL has ten Associated Partners (as at 2017)

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 Member Institutions and Sites



Associate Partners of the DZL

- Asklepios Clinic Munich-Gauting
- CAPNETZ STIFTUNG
- COSYCONET (German COPD and Systemic Consequences – Comorbidities Network)
- The German National Cohort (NAKO)
- Pulmonary Research Institute
- PROGNOSIS (The Prospective German Non-CF-Bronchiectasis Registry)
- PROGRESS (Pneumonia Research Network an Genetic Resistance and Susceptibility for the Evolution of Severe Sepsis)
- Robert Koch Institute
- University Clinic Schleswig Holstein, Kiel Campus
- University Clinic Schleswig Holstein, Lübeck Campus

DZL Site Borstel, Lübeck, Kiel, Grosshansdorf

Airway Research Center North (ARCN)

Partner Institutions of the 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 LungenClinic Grosshansdorf

Prof. Dr. Klaus F. Rabe



- Director of the DZL Site ARCN
- Medical Director of the LungenClinic Grosshansdorf
- Professor of Pneumology, Christian-Albrechts-University, Kiel
- Chairman of the Institute for Lung Research (ILF)
- President of the European Respiratory Society (ERS) 2011/2012
- Fellow of ERS (FERS)
- President of the German Society for Pneumology and Respiratory Medicine (DGP) 2017 – 2019

Contact

DZL Site Coordinator, ARCN:
 Dr. Jörn Bullwinkel
 E-Mail: j.bullwinkel@lungenclinic.de
 Tel.: +49 (0)4102 601-2410

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 causes of lung diseases and are committed to developing novel imaging techniques. Cohort projects and clinical studies are conducted together with the Pulmonary Research Institute 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 (BREATH)

Partner Institutions of the Site

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

Prof. Dr. Tobias Welte



- Director of the DZL Site BREATH
- Chairman of the German Sepsis Society
- Speaker for the Clinical Study Center Hannover (KS-MHH)
- 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 Society for Pneumology and Respiratory Medicine (DGP) 2013–2015
- Vice-President of the European Respiratory Society (ERS) 2016/2017, ERS President Elect 2017/2018, ERS President 2018/2019
- Fellow of ERS (FERS)
- Fellow of ERS (FERS), elected in 2014

Contact

DZL Site Coordinator, BREATH:
Dr. Annegret Zurawski
E-Mail: Zurawski.Annegret@mh-hannover.de
Tel.: +49 (0)511 532-5192

Research Profile

The focus of BREATH is the translation of findings from basic research into clinical practice, with regard to all topics listed below. This includes the execution of clinical studies of all phases relevant for registration and 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. Preclinical 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 Site

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

Prof. Dr. Dr. h.c. Erika von Mutius



- Director of the DZL Site CPC-M
- Head of the Department Asthma and Allergy at the Dr. von Hauner Children's Hospital of the Ludwig-Maximilians-University Munich
- Member of the Editorial Board of the New England Journal of Medicine (since 2006)
- Recipient of the Gottfried Wilhelm Leibniz Prize from the German Research Foundation
- Holder of the Cross of Merit of the Federal Republic of Germany
- Fellow of ERS (FERS)

Contact

DZL Site Coordinator, CPC-M:

Dr. Antje Brand

E-Mail: antje.brand@helmholtz-muenchen.de

Tel.: +49 (0)89 3187-4698

Research Profile

At the Comprehensive Pneumology Center Munich (CPC-M), the Helmholtz Zentrum München – German Research Center for Environmental Health, Ludwig-Maximilians-University Munich with its University Hospital and the Asklepios Clinic Munich-Gauting have come together to form one of the largest centers in the world for translational research on chronic lung disease. The Helmholtz Zentrum München is a renowned expert in linking fundamental research and applied medical research. Ludwig-Maximilians-University is one of the top-level universities in the German Excellence Initiative. Its medical faculty is involved in high-level pulmonary research and medical care. The Asklepios Clinic Munich-Gauting is one of the leading hospitals in Germany that specializes in lung diseases. Research at CPC-M is focused on chronic lung diseases. CPC-M scientists integrate state-of-the-art techniques in molecular and cell biology, pharmacology, molecular pathology and clinical medicine in order to develop new diagnostic tools and therapies. In addition to the research program, CPC-M scientists are coordinators for the Disease Areas “Interstitial Lung Disease” and “Asthma and Allergy”. As an important link between clinical and basic research, the CPC-M also runs a research clinic. Here, clinicians and scientists work closely together to connect research results with therapeutic approaches. 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 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

DZL Site Coordinator, TLRC:
Dr. Birgit Teucher
E-Mail: Birgit.Teucher@med.uni-heidelberg.de
Tel.: +49 (0)6221 56-4296

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 (CF), 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 diagnostics 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 immunobiology 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 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)
- Director of the DZL site 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)

Contact

DZL Site Coordinator, UGMLC:
 Dr. Sylvia Weißmann
 E-Mail: sylvia.weissmann@ugmlc.de
 Tel.: +49 (0)641 99-42411

Research Profile

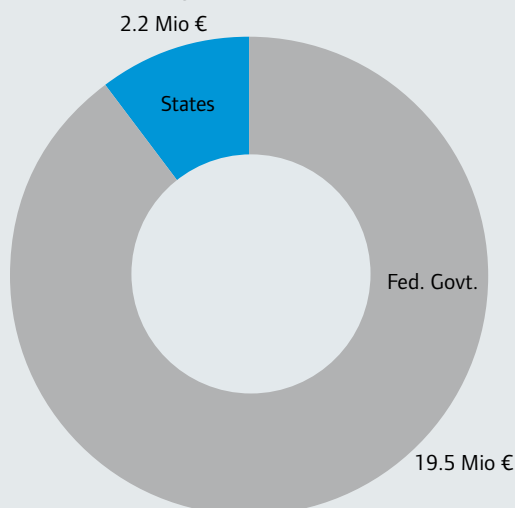
Translational research at the Universities of Giessen and Marburg Lung Center (UGMLC) focuses on lung diseases caused by inflammatory and hyperproliferative processes. This includes research on the antenatal and postnatal impact of environmental factors on the development of Asthma as well as on the development and therapy of Chronic Obstructive Pulmonary Disease (COPD), with particular 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 Diffuse Parenchymal Lung Disease (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 Excellence Cluster Cardio-Pulmonary System (ECCPS). Within the DZL, UGMLC hosts the DZL Head Office as well as the DZL Biobank and Data Management Platform.

Finance and Personnel

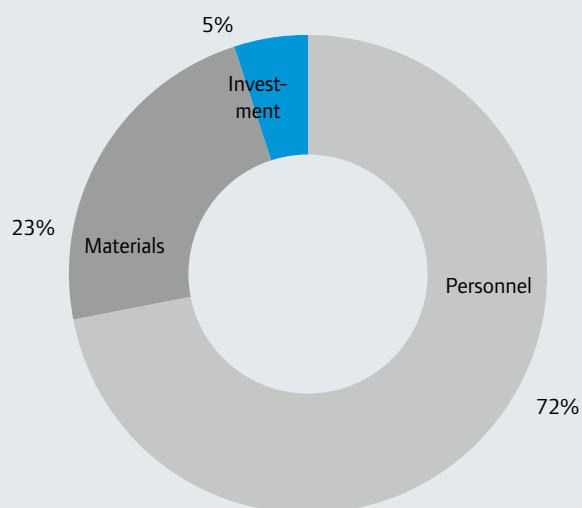
Total Funding and Cost Breakdown

The total funding for the DZL in 2016 was € 21.7 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. Finance is managed by DZL Funding Management located at Helmholtz Zentrum Munich. The Funding Management forwards the project funds to the DZL partner institutions. (As of July 2017)

Total Funding 2016



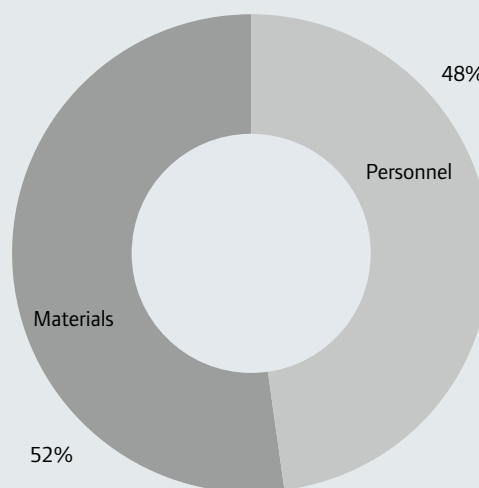
Cost Breakdown: DZL Expenses 2016



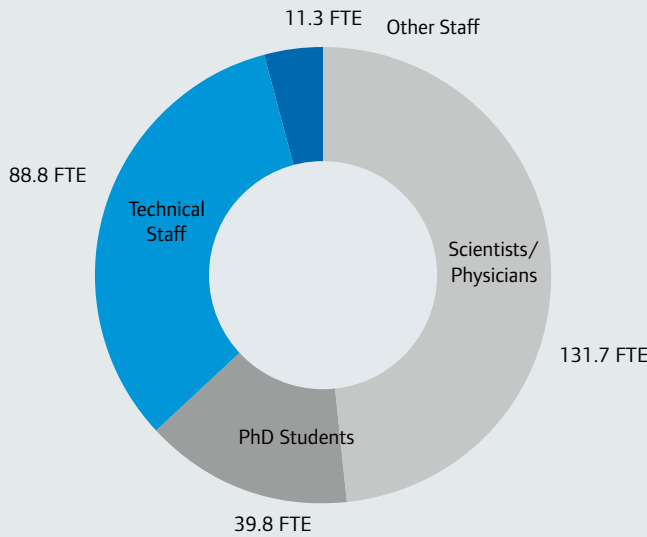
Cost Breakdown – DZL Expenses 2016 (as at July 2017)

The DZL e.V. is financed through membership fees collected from each member institution. As in previous year, this amounts to € 500,000 in 2016. The 2016 Annual Financial Statement and Year-end Close of the DZL e.V. was conducted by the firm Haas & Haas (Giessen).

Cost Breakdown: DZL e.V. Expenses 2016

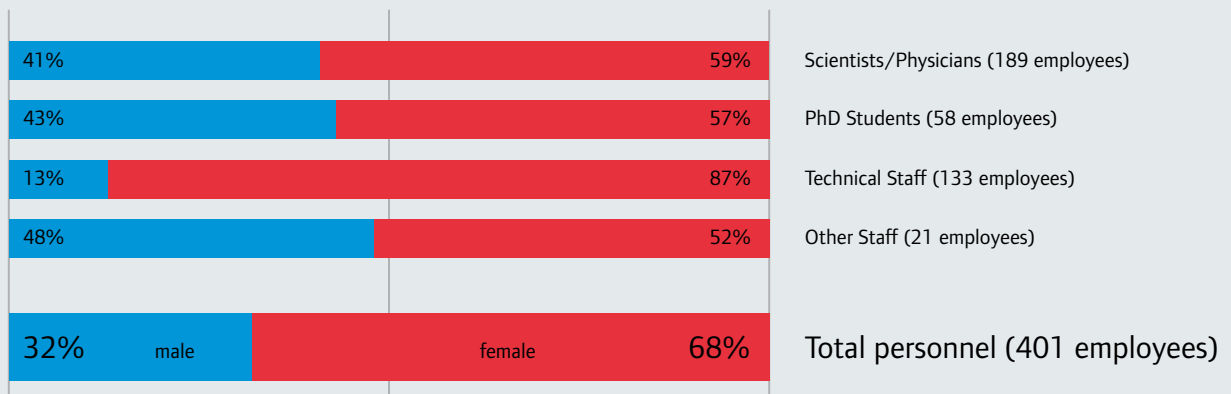


Personnel and Gender Equality

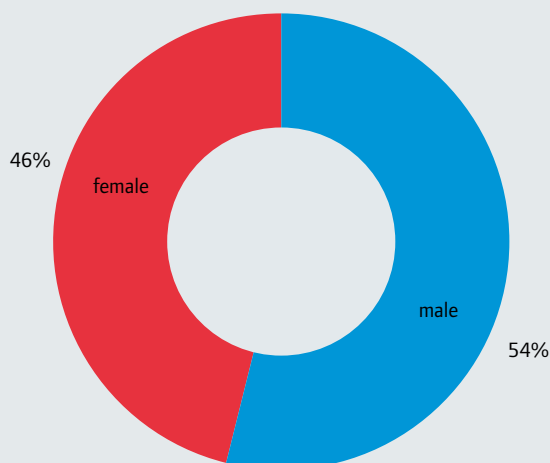


Personnel and Gender Equality – DZL 2016

In 2016, 401 employees (271.6 Full-Time Equivalents) were directly financed with DZL funds across the five partner centers. Of the 401 funded employees, 271 are women (68%).



Professorships and Leaders of Junior Research Groups



Professorships and Leaders of Junior Research Groups

In 2016, there were 13 professorships and leaders of junior research groups funded within the DZL, 6 of them women (46%).

Masthead

Publisher

Deutsches Zentrum für Lungenforschung (German Center for Lung Research, DZL) e. V.

Head Office

Aulweg 130, 35392 Giessen, Germany

Phone: +49 (0)641 99-46721, email: contact@dzl.de, Homepage: www.dzl.de

Board of Directors

Prof. Dr. H. Werner Seeger (Chairman), Prof. Dr. Marcus A. Mall, Prof. Dr. Klaus F. Rabe,
Prof. Dr. Erika von Mutius, Prof. Dr. Tobias Welte

Managing Director

Dr. Christian Kalberlah

Editors/Authors

Dr. Christian Kalberlah and Prof. Dr. Werner Seeger (Chief Editors), Sabine Baumgarten, Susanne Klasen, Staff of the Disease Areas and Platforms/Departments incl. Managers and Directors of the DZL sites.

Project Management/Research

Dr. Christian Kalberlah, Sabine Baumgarten, Susanne Klasen

Photos/Graphics

DZL/DZL partners, unless otherwise specified; cover: fotolia/Evtstratenko Yuliya; S. 3: iStock; S. 34: reprinted with permission of the American Association for Cancer Research, from: Marwitz et al. (2016) Downregulation of the TGFbeta Pseudoreceptor BAMBI in Non-Small Cell Lung Cancer Enhances TGFbeta Signaling and Invasion. *Cancer Res* 76: 3785-3801; S. 44: fotolia/Science RF; S. 51: fotolia/alotofpeople; S. 63: Till Budde.

Editorial Comment

Insofar as the masculine form is used in the contents of this report, it is assumed that this refers to both genders on equal terms.

The DZL is funded by



Bundesministerium
für Bildung
und Forschung



Baden-Württemberg

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Deutsches Zentrum für Lungenforschung (German Center for Lung Research, DZL) e. V.

Head Office

Aulweg 130 | 35392 Giessen | Germany

contact@dzl.de

www.dzl.de

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