

German Center for Lung Research

ANNUAL REPORT



2018

Giant "Lung" Jellyfish off the British Coast

Translational Research to Combat Widespread Lung Diseases

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Foreword



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Prof. Dr. Tobias Welte
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Have stamina and adopt a long-term perspective—to bring it down to its simplest level, this was a recommendation of the German Council of Science and Humanities (Wissenschaftsrat) when it gave the German Centers for Health Research (DZG) excellent marks and took a stand on the further development of the DZG in 2017. In 2018, the strategic work of the German Center for Lung Research (DZL) was based entirely on this theme, involving mainly three interdependent levels.

A long-term perspective for our patients: This is the goal of all DZL scientists and physicians. In Germany, every four minutes a person still dies from lung or airway diseases. This is mostly due to Chronic Obstructive Pulmonary Disease (COPD), pulmonary infections (primarily pneumonia and tuberculosis), and lung cancer. All these diseases are among the top 10 global causes of deaths; the World Health Organization (WHO) estimates that they are responsible for almost 16 million deaths each year. To address these challenges productively, there is a need for cooperation of the leading lung researchers in this country.

A long-term perspective for our researchers: Our scientists and physicians need solid structures that enable them to achieve even better diagnostic and therapeutic outcomes. It is important to develop these structures with an eye to future prospects and strengthen partnerships where lung research overlaps with cancer, cardiovascular, infection, or diabetes research, for example.

A long-term perspective for translational research: The DZL was founded based on this idea, knowing that translational research requires a reasonable period of time to achieve well-developed and effective results. The prerequisites for this are a solid foundation and a long-term prospect for the benefit of our patients.

We invite you to let us guide you through our current research projects and achievements, and continue to be a companion of the DZL with stamina in the future.

Giessen/Heidelberg/Grosshansdorf/Munich/Hanover in July 2019
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 240 principal investigators and their research groups work together to combat respiratory disease through translational research. Twenty-nine 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 Lung Injury, 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

Asthma is the most prevalent chronic respiratory disease in children and is also very common in adults. Although the clinical manifestations of asthma in children and adults are rather uniform (e.g. wheezing, shortness of breath, and cough), population-based clinical and genetic studies suggest that asthma is not one but many diseases. Thus, a single “one-size-fits-all” treatment approach is unlikely to work to tackle this important

health problem. In order to design personalized treatment approaches for asthma patients, there is urgent need to elucidate the particular molecular mechanisms underlying the various types of asthma. The decoding of such mechanisms and their translation to the individual patient is the aim of the Disease Area Asthma and Allergy of the DZL.

Goals Achieved in 2018

- ✓ 15 joint publications of several DZL sites
- ✓ Design of a study on specific immunotherapy as a preventative action in early childhood (supported by the DZL Clinical Trial Board)
- ✓ 300 additional study visits in the ALLIANCE asthma cohort (400 study visits, 450 incl. phone visits)
- ✓ 10 projects for using the biomaterial and accompanying data collected (11 projects started)

Goals for 2019

- 15 joint publications of several DZL sites
- 450 additional study visits in the ALLIANCE asthma cohort
- 15 ongoing projects for using the biomaterial and accompanying data collected
- Development of a DZL infrastructure for experimental microbiome research

Disease Area Leaders

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Administrative Coordinator of the Disease Area

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Participating DZL Partner Sites

all

Research Highlight 2018

Monitoring Asthma Therapy: Do We Have to Go Down to the Lungs or Will the Nose Suffice?

Effective monitoring of the course of a disease is key to individually adapted therapy. Therefore, the search for biomarkers, which provide physicians with information on the current development of a patient's disease, plays a major role for many chronic conditions. Regarding research carried out at the DZL, this involves the area of asthma. An aggravating factor in this case is that the lungs, which are the most affected part by the disease, are not easy to access: Bronchoscopy is far too burdensome and cannot be integrated easily into an asthmatic patient's daily life. Sputum collection, too, requires a considerable amount of time. Biomarkers obtained through minimally invasive or non-invasive methods, e.g. from blood or nasal secretion, would be more favorable. This would only require us to take a blood sample or nasal swab, which could be done conveniently during a visit at the doctor's office.

The hypothesis that the lower airways and the upper airways (nasopharynx) are connected by more than just air has existed for years. According to this "united airway hypothesis", imprinting of the immune system of the lower airways is also reflected in the upper airways. DZL scientists of the CPC-M and ARCN sites have recently investigated this matter by comparing nasal secretion and sputum. They examined asthmatic patients during and out of the grass pollen season as well as healthy subjects. The scientists compared a whole range of messengers, called cytokines, as well as immune cells from the sputum.

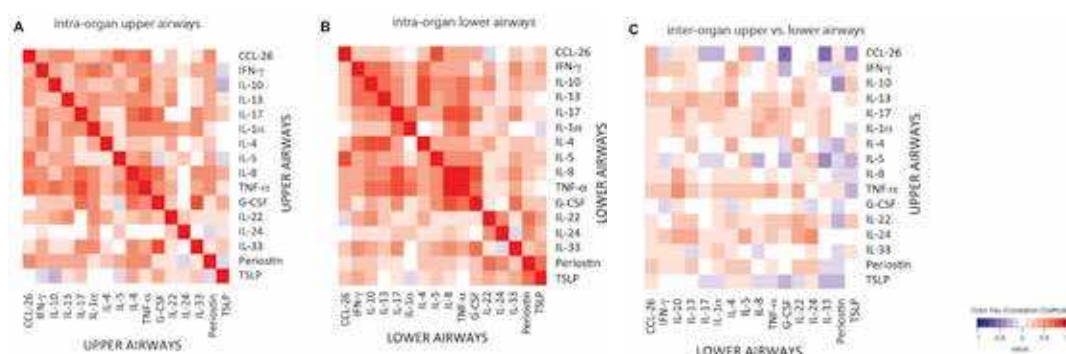
The findings published in the *Journal of Allergy and Clinical Immunology* have shown that the patterns of different cytokines in the upper and lower airways are similar. The comparability between the upper and lower airways expected according to the united airway hypothesis was mainly observed for proallergic cytokines. For instance, levels for epithelial interleukin 24 (IL-24) are very similar, so this cytokine could be used as a representative for the lungs.

IL-24 also showed correlations to therapy control of the patients, which were identified based on questionnaires: Higher IL-24 levels result in poorer control of the symptoms of the disease. In asthmatic patients, IL-24 levels were significantly increased during grass pollen season when compared with out-of-season levels. Furthermore, there was a correlation between IL-24 and regulatory T cells. In asthmatic patients, there was a decrease in the number of these cells, which is consistent with previous studies.

The scientists now want to investigate the most promising findings in larger studies. A further result might be a better understanding of the different types of asthma, which are characterized by very different patterns. This is another key objective of the ALL Age Asthma Cohort (ALLIANCE) of the DZL.

Further Information:

✉ Zissler UM, Ulrich M, Jakwerth CA, Rothkirch S, Gueth F, Weckmann M, Schiemann M, Haller B, Schmidt-Weber CB, Chaker AM (2018) Biomatrix for upper and lower airway biomarkers in patients with allergic asthma. *J Allergy Clin Immunol* 142: 1980-1983



Biomarker grids reflecting correlations between upper and lower airways cytokine levels. Intraorgan correlations for upper (A) and lower (B) airways and interorgan correlations (C) were depicted by using respective correlation coefficients (r) from negative (dark blue) to positive (red) values. Intraorgan correlations seemed to be predominantly strong, whereas interorgan relations were most visible by using nasal and sputum IL-24 measurements.



Chronic Obstructive Pulmonary Disease (COPD)

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.

Goals Achieved in 2018

- ✓ Clinical studies on GATA3 and iNOS-EMAPII completed (GATA3: published; iNOS-EMAPII: not yet completed)
- ✓ 15 joint publications of several DZL sites (21 publications)
- ✓ Conference calls every two months for research coordination
- ✓ Start of a project on cardiovascular effects with the Hamburg City Health Study
- ✓ Start of a project in collaboration with the German Center for Cardiovascular Research (DZHK) on cardiovascular biomarkers in COPD patients (project on hs-troponin)

Goals for 2019

- Completion of the iNOS-EMAPII study (see above)
- 20 joint publications of several DZL sites
- Conference calls every two months for research coordination
- Start of the second recruitment period of COSYCONET
- Manuscript across all Disease Areas with ALLIANCE registry of DA AA on breathomics

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.

Disease Area Leaders

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Participating DZL Partner Sites

all

Research Highlight 2018

Can COPD Be Stopped?

In general, COPD is a preventable disease caused by cigarette smoke or air pollution. Due to emphysema and chronic inflammation, COPD patients suffer from gradual deterioration in pulmonary function, which makes breathing increasingly difficult. Effective therapeutic options are currently not available. The group of Ali Önder Yildirim at the DZL site CPC-M investigates how the immune system of COPD patients changes and how it can be affected for treatment. The scientists published their latest findings in the specialist journal *EMBO Molecular Medicine*.

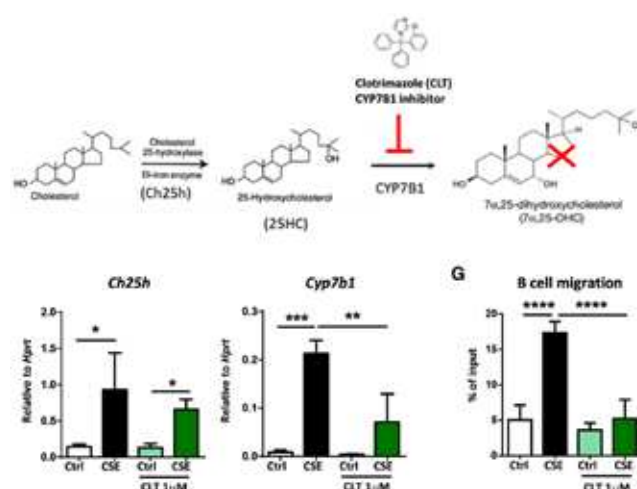
Chronic airway inflammation in COPD patients is often associated with the formation of characteristic lymphoid structures known as iBALT (Inducible Bronchus-Associated Lymphoid Tissue). iBALT contains B cells, which are mainly responsible for producing antibodies during an immune response. However, it remains unclear to what extent they contribute to the development of COPD. In their new study, DZL scientists investigated the effect of B cells and iBALT on COPD in detail. For this purpose, they examined cigarette-smoke-exposed mice over a longer period of time as well as tissue samples taken from COPD patients. Oxysterol metabolism is crucial to the development of iBALT and B-cell recruitment in these structures. Smoke or its components trigger the metabolism locally in lung airway cells. In two steps, the enzymes CH25H and CYP7B1 first convert the basic substance cholesterol into a dihydroxysterol, which binds to the receptor EBI2 expressed in B cells and sort of “lures” it into the iBALT. The DZL scientists found elevated levels of both enzymes in the lungs of COPD patients as well as in cigarette-smoke-exposed mice. Now the question was whether this process could be suppressed. In fact, animals in which the enzyme CH25H was switched off only developed little emphysema and iBALT after being exposed to cigarette smoke. Switching off the receptor EBI2, B cells continue to migrate into the lungs, where they are activated, but no longer develop iBALT structures. Interestingly, the pathological process could also be stopped in a different way: When treating the mice with the substance clotrimazole, which inhibits the involved enzyme CYP7B1, significantly less iBALT was found. Furthermore, no new emphysema developed. It is still unclear whether the substance also affects the recruitment of other immune cells. However, the authors demonstrated that B cells are responsible for the development of cigarette-smoke-induced emphysema observed here. The pharmacological modulation of the oxysterol metabolism might also be a research area for other diseases involving the formation of iBALT. This pathway

seems to be more promising than complete B-cell deactivation, which weakens the entire immune defense.

Now the DZL researchers want to investigate in a clinical study whether COPD patients can be helped with medication by suppressing the formation of iBALT in the lungs and restricting B-cell function specifically.

Further Information:

✉ Jia J, Conlon TM, Sarker RSJ, Taşdemir D, Smirnova NF, Srivastava B, Verleden SE, Güneş G, Wu X, Prehn C, Gao J, Heinzemann K, Lintelmann J, Irmeler M, Pfeiffer S, Schlöter M, Zimmermann R, Hrabě de Angelis M, Beckers J, Adamski J, Bayram H, Eickelberg O, Yildirim AÖ (2018) Cholesterol metabolism promotes B-cell positioning during immune pathogenesis of chronic obstructive pulmonary disease. *EMBO Mol Med* 10: e8349



Above: In two steps, the enzymes CH25H and CYP7B1 first convert Cholesterol into the active substance Dihydroxysterol (7α,25-OHC), which is responsible for B cells to migrate into the iBALT. With Clotrimazole (CLT) the CYP7B1 can be inhibited and the process can be interrupted.

Below: In mice exposed to cigarette smoke, both enzymes CH25H and CYP7B1 show increased expression. In control groups not exposed to cigarette smoke, the concentration of both enzymes is decreased. In mice treated with Clotrimazole (CLT), less enzymes are formed. Subsequently the migration of B cells into the iBALT decreases significantly.



Cystic Fibrosis (Mucoviscidosis)

Cystic Fibrosis (CF) is the most common genetically determined, early onset and still lethal disease. CF affects approximately one in 2,500 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.

Goals achieved in 2018

- ✓ Complete Orkambifacts® recruitment (Clinical Trial prolonged for the recruitment of paediatric patients)
- ✓ 600 patients registered in the CF register
- ✓ Metagenomic pipeline for non-CF diseases established
- ✓ Association dataset (airway microbial metagenome/CF disease severity) created
- ✓ Clinical trial to investigate the efficacy of a new antiinflammatory therapy with Anakinra to treat CF was launched (Start date postponed 2019)
- ✓ Start of the first controlled and randomised clinical trial for the evaluation of the efficacy of the CF modulators Lumacaftor and Ivacaftor in toddlers, in cooperation with Vertex Pharmaceuticals

Disease Area Leaders

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ARCN, BREATH, TLRC, UGMLC

Research Highlight 2018

Direct impact of combination therapy on CFTR-function in Cystic Fibrosis

In people with Cystic Fibrosis (CF), various mutations in the CFTR gene (cystic fibrosis transmembrane conductance regulator gene) prevent cells to regulate their salt-water-balance via chloride ion channels in the epithelial cell wall. Without the chloride to attract water to the cell surface, the mucus in various organs, in particular the lungs, becomes very thick and sticky. Mucus clogging the airways causes the following symptoms: persistent cough, shortness of breath, infections and inflammation. Although we have made progress in treating these symptoms, there is still no cure.

With the advent of the development of so-called CFTR-modulators in 2011, it was for the first time possible to directly treat the basic defect of CF. In patients with so-called CFTR-gating mutations for whom the main defect lies with the defective opening of the channel on the cell surface, the drug ivacaftor (a CFTR-potentiator) binds to and potentiates the channel opening ability of CFTR proteins on the cell surface, which results in a partial compensation of loss of function. However,

it to the cell surface. The drug lumacaftor (a CFTR-corrector) prevents the premature destruction of the protein, resulting in increased processing and trafficking of mature protein to the cell surface. In combination with ivacaftor the probability increases that the defective channel will open and allow chloride ions to pass.

Preceding studies demonstrated that an ivacaftor/lumacaftor combination therapy can slow down the progression of CF disease but these studies did not investigate the evidence for a direct effect on the basic defect. The DZL sites Hanover, Gießen and Heidelberg now reported for the first time the direct impact of combination therapy on the *in vivo* correction of CFTR-function. The treatment increased CFTR channel activity by an average of 15%, as determined by the CFTR biomarkers sweat chloride, nasal potential difference (NPD) and intestinal current measurement (ICM) in rectum biopsies. This level of improvement roughly corresponds to a CFTR-function equivalent to what is observed in patients with CFTR residual function.

Goals 2019

- Elucidation of the CF airways microbiome
- Evaluation of the efficacy of pulmonary transfer of host defense cells for the treatment of acute airway infections with *P. aeruginosa* in a pre-clinical model
- Impact of gene – gene interactions on the CF disease modifying activity of the epithelial sodium channel ENaC
- Search for novel compounds that activate the alternative chloride channels SLC26A9 by high-throughput screening
- Elucidate the role of Interleukin-17 (IL-17) in the pathogenesis of CF lung disease
- Study the role of diverse proteases as biomarker of lung disease activity in CF
- Recruitment completion of the Lumacaftor / Ivacaftor clinical trial (see above)

patients with the most frequent mutation of the CFTR-gene, the Phe508del mutation, do not benefit from ivacaftor as the sole treatment.

In Germany, about 90% of all CF patients carry the Phe508del mutation that causes abnormal folding and trafficking of CFTR to the epithelial cell membrane, and also abnormal opening of the channel in the limited amounts of protein that make

Taking into account the short duration of treatment in this study, the lack of correlation between the observed improvement in CFTR-function and standard clinical outcome measures such as ‘forced expiratory volume in one second’ (FEV1, a measure of lung function) and body mass index (BMI) can most likely be explained by the greater variability of these clinical endpoints. Thus the CFTR biomarkers may be more robust than clinical outcome measures in detecting the clinical short-term benefit of *in vivo* CFTR modulator therapy.

Results of this study were published in the *American Journal of Respiratory and Critical Care Medicine*.

Further Information:

📄 Graeber SY, Dopfer C, Naehrlich L, Gyulumyan L, Scheuermann H, Hirtz S, Wege S, Mairbäurl H, Dorda M, Hyde R, Bagheri-Hanson A, Rueckes-Nilges C, Fischer S, Mall MA, Tümmler B. (2018) Effects of Lumacaftor/Ivacaftor Therapy on CFTR Function in Phe508del Homozygous Patients with Cystic Fibrosis *Am J Respir Crit Care Med*; 197(11): 1433-1442



Pneumonia and Acute Lung Injury

Goals Achieved in 2018

- ✓ Establishment of a bronchoalveolar lung organoid *in-vitro* model for high-resolution display of infection processes as well as lung damage and repair
- ✓ Definition of molecular mechanisms of macrophage-stem cell interaction in pulmonary repair after severe pneumonia for future therapeutic use (project completion expected for 2019)
- ✓ Completion of recruitment for cohort 1 of the GI-HOPE study
- ✓ Establishment of a cross-DZG project with the German Center for Infection Research

Goals for 2019

- *In-vivo* project on disease-specific reprogramming of bone-marrow-derived mesenchymal stem cells to treat pneumonia/ARDS
- Definition of the molecular mechanisms driving functional loss of macrophage host defense during severe viral pneumonia
- Completion of recruitment of the PROGRESS cohort (n=2,300 patients) and of the PROGNOSIS cohort (n=1,250 patients)
- Start of recruitment of the global CIGMA phase III trial on immunoglobulin treatment of patients with severe pneumonia

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.

Scientific Coordinators of the Disease Area

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Participating DZL Partner Sites

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Research Highlight 2018

Angiopoietin Ang-1: Biomarker and therapeutic approach at once?

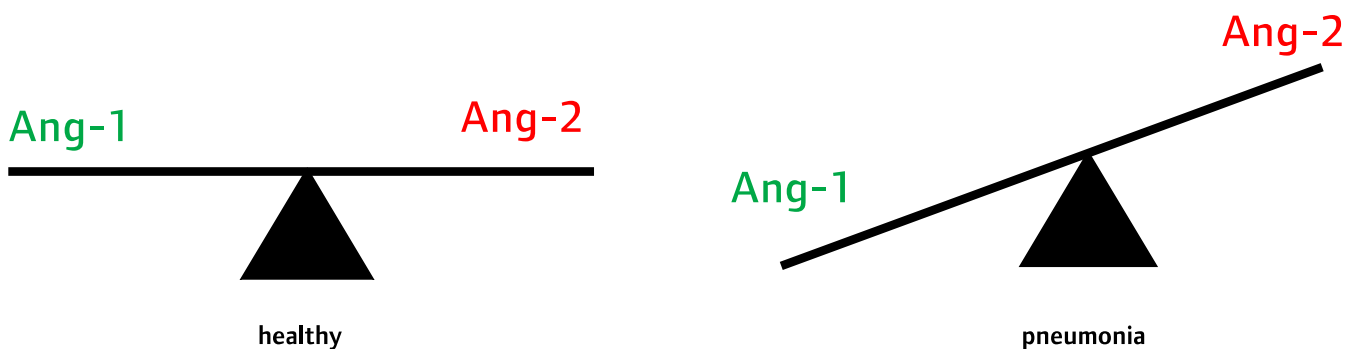
Pneumonia may evoke disruption of pulmonary endothelial barrier integrity, resulting in acute lung injury and lung failure despite antibiotic therapy. Treatment of acute lung injury is mainly supportive, because key elements of inflammation-induced barrier disruption remain undetermined. The deleterious effects of pneumonia can be attributed to both direct effects of pathogenic factors and uncontrolled host response. Among host factors, recruitment of polymorphonuclear neutrophils, increased release of pro-inflammatory cytokines, and other, partly unidentified factors may contribute to the pathogenesis of pneumonia. As host factors, angiopoietins Ang-1 and Ang-2 as well as their receptor tyrosine kinase (Tie2) are involved in the regulation of vascular permeability and inflammation; however, their role in pneumonia remains unknown. The study thus aimed to investigate the prognostic and pathogenic impact of angiopoietins on regulating pulmonary vascular barrier function and inflammation in bacterial pneumonia.

The analysis of samples from the CAPNETZ and PROGRESS cohorts showed that barrier-stabilizing Ang-1 decreased and its counterpart Ang-2 increased in the serum of patients with pneumonia. Ang-2 serum levels predicted mortality and length of hospital stay, improving the predictive value of the CURB-65 score (recommended by international guidelines as a predictor for mortality in pneumonia).

In an experimental model, pulmonary Ang-1 similarly decreased and Ang-2 increased, with Ang-2 contributing to lung barrier dysfunction in pneumococcal pneumonia. Therapeutic administration of Ang-1 in this model reduced lung permeability and inflammation. Thus, targeting the Ang-/Tie2 system may provide a therapeutic perspective for the prevention of acute lung injury in pneumonia.

Further Information:

✉ Gutbier B, Neuhauß AK, Reppe K, Ehrler C, Santel A, Kaufmann J, Scholz M, Weissmann N, Morawietz L, Mitchell TJ, Aliberti S, Hippenstiel S, Suttrop N, Witzernath M; CAPNETZ and PROGRESS Study Groups. Prognostic and Pathogenic Role of Angiopoietin-1 and -2 in Pneumonia (2018) Am J Respir Crit Care Med.198(2):220-231



An Ang-1 therapy counterveils the negative effect of Ang-2. A high concentration of Ang-2 in Pneumonia results in a higher level of mortality.



Diffuse Parenchymal Lung Disease (DPLD)

Diffuse Parenchymal Lung Disease (DPLD), or Interstitial Lung Disease (ILD), comprises a group of over 200 different disorders, which are mainly characterized by progressive scarring of the lung architecture and often result in respiratory failure. DPLD occurs in children and adults secondary to acute or chronic lung injury provoked by the inhalation of toxic gases or dusts, as part of systemic diseases (e.g. connective tissue disorders), or as a result of therapeutic measures (e.g. mechanical ventilation or chemotherapy). In a significant proportion of patients, however, the cause remains unknown; this is called Idiopathic Interstitial Pneumonia (IIP), which also comprises Idiopathic Pulmonary Fibrosis (IPF).

Although different in origin, the course of many DPLDs is similar as the disease progresses and is associated with poor prognosis. Only in recent years have antifibrotic treatments for IPF become available. These do not entirely prevent the disease from progressing but may slow down scarring in the lungs, which can be prognostically relevant. The only curative treatment, however, is lung transplantation. To develop new diagnostic strategies and causal treatment options, it is indispensable to gain deeper insights into the early and essential underlying disease mechanisms. More specific and earlier identification of disease-relevant alterations, which makes it possible to assess the risks, should enable the development of individualized therapeutic concepts also in the field of DPLDs.

The DPLD Disease Area of the DZL brings together and increasingly links internationally renowned experts for both pediatric and adult forms of DPLD. This makes it possible to better identify reparative as well as regenerative processes and develop both diagnostic and therapeutic options, from the newborn to the elderly patient.

[Scientific Coordinators of the Disease Area](#)

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BREATH, CPC-M, TLRC, UGMLC

Research Highlight 2018

Mechanism of Fibrosis Development Discovered

Pulmonary fibrosis is associated with the increased formation of connective tissue in the lungs, resulting in scarring (fibrosis) of functional lung tissue. This leads to a decrease in the inner surface of the extremely fine alveoli and the extensibility of the lungs, which, in turn, impedes the intake of oxygen and the release of carbon dioxide. The result is impaired lung function. IPF is a particularly aggressive form of the disease, which cannot be attributed to a specific cause. Symptoms rapidly get worse. Existing drugs can slow the progression of the disease but are unable to stop it permanently.

Research therefore continues to focus on elucidating the mechanisms underlying the pathological tissue changes associated with IPF. One approach that has been intensively pursued for several years now in the Lung Repair and Regeneration Research (LRR) Unit and the Institute of Lung Biology and Disease (ILBD) at the Helmholtz Center in Munich aims to influence the WNT signaling pathway. It is already known that the signaling molecule WNT5A is responsible for stimulating the proliferation of connective tissue cells in the lungs.



Extracellular vesicles

The LRR Research Group headed by Dr. Dr. Melanie Königshoff has found that extracellular vesicles are also very likely to be involved in IPF. Simply put, extracellular vesicles are tiny pouches released by cells that can contain a large number of messenger substances, such as proteins and nucleic acids. They are an important means of communication between cells and organs and help ensure that the substances reach completely new sites.

Until recently, it was unclear whether and how extracellular vesicles are involved in IPF. In this study, the researchers showed that increased levels of extracellular vesicles occur in IPF patients, which then act as carriers of WNT5A. The scientists were also able to confirm these results in an experimental model. What is more, the authors showed in Petri dish experiments that reducing the number of vesicles decreased tissue scarring.

In further preclinical studies, the researchers now want to examine the suitability of extracellular vesicles as a pharmacological biomarker as well as a possible therapeutic target.

Goals Achieved in 2018

- ✓ New strategies on clinical phenotyping of pediatric and adult DPLD cohorts
- (✓) Establishment of new clinical and interventional studies for neonatal and adult patients (some goals to be achieved in 2019)
- ✓ New disease models (*in vivo* and *ex vivo*)
- (✓) Development of markers and cellular therapies for initial epithelial damage and fibroproliferation (interactome atlas)

Goals for 2019

- Characterization of alternative macrophage activation, inflammasome, and programmed cell removal in DLPD considering environmental effects
- Characterization of epithelial cellular plasticity in neonatal and adult DPLD
- Establishment of an interventional study on IPF (with a focus on epigenetic reprogramming)
- Use of new experimental disease models incl. stem cell organoids, viral infection
- Characterization of epigenetic alterations in progressive DPLD (patient-specific/single-cell-specific)

Further Information:

✉ Martin-Medina A, Lehmann M, Burgy O, Hermann S, Baarsma HA, Wagner DE, De Santis MM, Ciolek F, Hofer TP, Frankenberger M, Aichler M, Lindner M, Gesierich W, Guenther A, Walch A, Coughlan C, Wolters P, Lee JS, Behr J, Königshoff M (2018) Increased Extracellular Vesicles Mediate WNT-5A Signaling in Idiopathic Pulmonary Fibrosis. *Am J Respir Crit Care Med* 198, 12: 1527–1538



Pulmonary Hypertension

Pulmonary Hypertension (PH) is a disease of the pulmonary vasculature, leading to shortness of breath, dizziness, fainting, and ultimately right heart failure. A total of approximately 100 million people worldwide suffer from one of the forms of Pulmonary Hypertension. Vascular pathology is characterized by vasoconstriction of the pulmonary vessels and abnormal (pseudomalignant) remodeling processes (thickening) of all vessel layers. 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 when it comes to recovering structural and functional lung vascular integrity, a prerequisite for symptom-free long-term survival. Restoration of the vascular structure and function (reverse remodeling) is the main goal of the research work carried out by the PH team.

Goals Achieved in 2018

- ✔ Assessment of the applicability of the Heidelberg Gene Panel to estimate the prognosis of patients with Pulmonary Arterial Hypertension (PAH), to be continued in 2019
- ✔ Protein profiling analysis (Sciomics) of PAH patients to identify subgroups with different response to therapy
- ✔ Initiation of and recruitment into a proof-of-concept study: inhaled paclitaxel for the treatment of PAH to be continued in 2019
- ✔ Publication of guidelines as a result of the 6th World Symposium on Pulmonary Hypertension (WHO conference)

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

Research Highlight 2018

Pulmonary Arterial Hypertension (PAH) is a devastating and life-threatening disease of the lung vasculature. It is characterized by rapid progression with poor prognosis, ultimately leading to right heart failure and death. The abnormal remodeling of the cellular structure of the small pulmonary arteries represents an important pathological characteristic of PAH. Excessive proliferation and resistance to cell death of different cell types lead to pulmonary vascular obstruction, causing an increase in pulmonary arterial blood pressure and right ventricle overload. In PAH patients, these vascular lesions affected by the remodeling process primarily consist of pulmonary arterial smooth muscle cells (PASMCs) with a hyper-proliferative, tumor-like phenotype. Unfortunately, currently available medication does not directly target the disease-triggering mechanism but rather focuses on vasodilation and/or relaxation.

Therefore, we have started a project to identify new drug targets for the treatment of PAH, looking for proteins involved in the aberrant signaling pathways leading to the observed hyper-proliferative, tumor-like phenotype of PASMCs. Phosphorylating enzymes, called kinases, are a group of proteins that are involved in these signaling pathways. Using a kinase activity screen, we identified a set of kinases, the cyclin-dependent kinases CDK4 and CDK6, which are over-activated in PASMCs of PAH patients. Blocking these enzymes (CDK4 and CDK 6) by a drug that has already been approved for the treatment of breast cancer (but not PAH) resulted in cell cycle arrest and thus reduced proliferation of PASMCs. Further experiments on the molecular level confirmed the inhibition of this particular signaling pathway. In two experimental models of PAH, palbociclib treatment resulted in the improvement of several pathophysiological parameters: Palbociclib reduced

pulmonary vascular remodeling, reversed the elevated right ventricular systolic pressure, reduced right heart hypertrophy, and finally restored the cardiac index.

The strong anti-proliferative profile of this approved CDK inhibitor suggests that palbociclib has the necessary properties to allow further investigation of its therapeutic benefit in PAH patients. This study was submitted to *Nature Communications* in 2018; after the revision process, it was accepted for publication in 2019.

For this excellent work, both first authors, Astrid Weiss and Moritz Neubauer, received the René-Baumgart award and were selected for an interview with Karger Kompass Pneumologie.

Further Information:

 Weiss A, Neubauer MC, Yerabolu D, Kojonazarov B, Schlueter BC, Neubert L, Jonigk D, Baal N, Ruppert C, Dorfmueller P, Pullamsetti SS, Weissmann N, Ghofrani HA, Grimminger F, Seeger W, Schermuly RT (2019) Targeting cyclin-dependent kinases for the treatment of pulmonary arterial hypertension. *Nature Communication* 10, Article number: 2204

Goals for 2019

- Analysis of the kinase profile of circulating cells and PAH lungs with the aim to develop advanced forms of treatment
- Development of new therapies for Pulmonary Hypertension caused by cigarette smoke and e-cigarette vapor
- Individualized treatment and monitoring of PAH using a new form of sensors (Single Point Cardiodynamics, SPC)
- Development of new inhalation strategies for the treatment of Pulmonary Hypertension with novel prostacyclin analogs, receptor agonists, or growth factor receptor inhibitors



End-Stage Lung Disease

Various acute and chronic lung disorders may 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) or lung transplantation. Today, however, ECMO therapy remains restricted to short-term application, primarily as a bridge to transplantation and as a bridge to recovery in acute pulmonary infections (e.g. H1N1). In chronic lung injury, transplantation remains the only

available therapy with the potential of true long-term survival. This treatment option, however, may only be used in a limited number of patients, excluding those with lung tumors, and long-term survival can be severely compromised by chronic rejection. Regenerative therapies that promote endogenous lung repair, cell transplantation, or tissue engineering are currently not available. The research program therefore 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.

Goals Achieved in 2018

- ✓ Preparation of position papers on organ donation (LTx) and post-transplantation (Tx)-Donor Management
- ✓ Prevention concept for post-Tx validated and highly-ranked published
- ✓ ELD project for ex vivo validation of stem cell therapies initiated

Goals for 2019

- Preparations for projects in the field of xenotransplantation of the lung
- First tests for an implantable gas exchange membrane (ICMO) in large animal model
- Specification of 3D histology of a pig lung for tissue printing

Scientific Coordinators of the Disease Area

Prof. Dr. Veronika Grau (UGMLC)

Prof. Dr. Axel Haverich (BREATH)

Administrative Coordinator of the Disease Area

Dr. Annegret Zurawski (BREATH)

Participating DZL Partner Sites

BREATH, CPC-M, UGMLC

Research Highlight 2018

Novel transport system for donor lungs reduces primary graft dysfunction after lung transplantation

Scientists at the DZL site BREATH were able to show that the transport and storage of donor lungs in a so-called Organ Care System (OCS) is possible and safe compared to the currently used standard procedure, storage at four degrees Celsius. The OCS is a mobile device in which donor lungs can be transported at body temperature while a blood-like solution flows through the explanted lung that also supplies nutrients. At the same time, the lung is “ventilated” in the OCS and can thus provide itself with oxygen. The device gives physicians at least twelve hours to transport the donor organ and assess and even improve lung function. For example, they can dry out liquid deposits or extract mucus.

The previous standard method for transport at four degrees Celsius grants the transplanters a maximum of ten hours. Due to a lack of blood and nutrient supply, the organ continuously deteriorates, which results in primary graft dysfunction in up to 30 percent of patients within the first 72 hours after transplantation. This worsens pulmonary function and may result in death of the patient.

In a large-scale, international randomized phase III study called INSPIRE, led by DZL researchers Axel Haverich and Gregor Warnecke, it was shown that the transport and storage in an OCS is not inferior to the conventional method of cooling. In addition, patients who received an OCS organ were much less likely to experience primary graft dysfunction than recipients of cooled organs.



Lungtransplantation – the only treatment option for some patients



Presentation of the Organ Care System (OCS)

Based on the results of the INSPIRE study, the OCS was approved in the US for the storage of lungs for transplantation in late March 2018. The results of the study were published in the journal *Lancet Respiratory Medicine* in 2018.

Further Information:

☑ Warnecke G, Van Raemdonck D, Smith MA, Massard G, Kukreja J, Rea F, Loo G, MD De Robertis F, Nagendran J, Dhital KK, Moradiellos Díez FJ, Knosalla C, Bermudez CA, Tsui S, McCurry K, Wang IW, Deuse T, Lesèche G, Thomas P, Tudorache I, Kühn C, Avsar M, Wiegmann B, Sommer W, Neyrinck A, Schiavon M, Calabrese F, Santelmo N, Olland A, Falcoz PE, Simon AR, Varela A, Madsen JC, Hertz M, Haverich A, Ardehali A (2018) Normothermic ex-vivo preservation with the portable Organ Care System Lung device for bilateral lung transplantation (INSPIRE): a randomised, open-label, non-inferiority, phase 3 study. *Lancet Respir Med* 6(5): 357–367



Lung Cancer

Goals Achieved in 2018

- ✓ Identification of integrin alpha-5 maturation as a therapeutic target for p53-mutated tumors
- ✓ Identification of a prognostic marker in squamous cell carcinoma for overall survival
- ✓ Genotyping of the prospective lung adenocarcinoma cohort
- ✓ Characterization of the clinical relevance of important molecular features of ALK patients
- (✓) Establishment of a pulmonary fibrosis/lung cancer cohort for multi-omics analysis

Goals for 2019

- Elucidation of mechanisms contributing to cell-context-specific regulation upon TGF- β stimulation in lung adenocarcinoma
- Pirfenidone as a TGF- β -inhibiting substance with potential as a therapeutic approach in NSCLC
- Characterization of the immunological microenvironment of ALK+ tumors
- Unravelling the effect of individual environmental carcinogens such as tobacco chemicals, tobacco smoke, and gamma radiation on the development of specific molecular subgroups of lung adenocarcinoma
- Identification of response biomarkers for metabolism-targeted cancer drug

Lung Cancer is among the most common types of cancer in Germany. The high mortality rate is often due to diagnosis at a late stage: 40% of Non-Small Cell Lung Cancer (NSCLC) patients present with metastases at the time of diagnosis. Advances in molecular tumor analysis have led to new opportunities to develop targeted therapies that act on specific molecular targets of the cancer cell. Besides chemotherapy and targeted therapy, 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, combined treatment approaches in precision medicine enable the application of the most effective treatment regimen for each patient. However, not all patients respond to targeted therapy or immunotherapy. Therefore, an important research goal is the identification of predictive markers indicating clinical response or potential treatment failure, for example through evidence of genetic tumor material towards biomarker-directed precision medicine.

Disease Area Leaders

PD Dr. Rajkumar Sava (UGMLC)

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Administrative Coordinator of the Disease Area

Dr. Birgit Teucher (TLRC)

Participating DZL Partner Sites

all

Understanding the Role of Specific Gene Fusions in Lung Cancer Progression

Anaplastic lymphoma kinase (ALK) is a protein formed primarily in the fetal and neonatal period that plays an important role in the development of the nervous system. Afterwards, it is rarely active in healthy tissue. Notably, in 5% of non-small cell lung cancer (NSCLC) patients, rearrangement of the ALK gene generates a novel ALK fusion protein that acts on downstream signaling pathway cascades to promote cell proliferation and tumor formation. Targeted substances for the treatment of these tumors are ALK-specific tyrosine kinase inhibitors (TKI), which block the overactive pathway by binding to the altered protein. Under sequential treatment with different TKI in combination with local therapies, metastasized lung cancer patients with an ALK alteration have the longest survival rate among lung cancer patients, with a median life expectancy that exceeds 5 years. However, the clinical course of the disease varies widely among these patients and was subject to the investigation reported here.

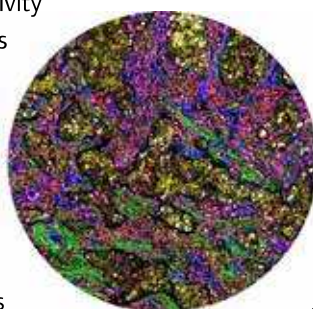
Lung cancer research groups at the Thoraxklinik Heidelberg, the Institute of Pathology at the University of Heidelberg, and the German Cancer Research Center (DKFZ) investigated the influence of the main fusion variants of the ALK gene (V1, V2, V3) on the course of the disease and response to treatment. 67 lung cancer patients with an altered ALK gene were retrospectively included in the analyses. It could be demonstrated that patients with the ALK variant V3 (about 1/3 of patients with ALK alteration) exhibited a higher number of metastases at the time of diagnosis, suggesting higher aggressiveness of the disease. In addition to that, a shorter period of time until disease progression under TKI treatment or chemotherapy and/or cerebral radiotherapy was characteristic in these patients. The life expectancy was reduced in comparison to patients with a V1/V2 variant. A possible explanation for the difference in the impact these variants have on the course of the disease is the special structure of the shorter variant 3, which exhibits higher biochemical stability as well as higher oncogenic signal activity and promotes increased cell mobility compared to variants 1 and 2.

The scientists also investigated how the TP53 tumor suppressor gene may impact disease progression in these patients. Mutations in this cellular repair gene constitute the most common genetic modification in all types of cancer, and about half of all NSCLC patients carry this mutation. The analysis of 102 metastasized (stage IV ALK+) lung cancer patients showed that the simultaneous presence of the high-risk variant V3 and TP53 gene mutation

is associated with the highest degree of metastases at the time of diagnosis, the fastest disease progression under TKI therapy, and the shortest overall survival. The findings of this study allow us to differentiate between patient subgroups: Patients with the V1 or V2 gene variant and intact TP53 gene benefit longer from TKI therapy than those with the aggressive V3 variant and/or TP53 mutation. This new understanding of ALK variants may contribute to the development of more effective treatment options for NSCLC ALK+ patients in the future.

Further Information:

- ✉ Christopoulos P et al. (2018). EML4-ALK fusion variant V3 is a high-risk feature conferring accelerated metastatic spread, early treatment failure and worse overall survival in ALK+ non-small cell lung cancer. *Int J Cancer*. 2018 Jun 15;142(12):2589-2598.
- ✉ Christopoulos P et al. (2018) EML4-ALK V3, treatment resistance, and survival: refining the diagnosis of ALK+ NSCLC. *J Thorac Dis*. 2018 Jun; 10(Suppl 17): S1989–S1991.
- ✉ Christopoulos P et al. (2019) Identification of a highly lethal V3+ TP53+ subset in ALK+ lung adenocarcinoma. *Int J Cancer*. 2019 Jan 1;144(1):190-199.
- ✉ Christopoulos P et al. (2019) Detection of TP53 Mutations in Tissue or Liquid Rebiopsies at Progression Identifies ALK+ Lung Cancer Patients with Poor Survival. *Cancers (Basel)*. 11(1): Article 124.



A composite image of a tissue micro array (TMA) of human lung cancer tissue with multiplex staining. This method could ultimately be used to characterize the tumor microenvironment of patients who have been treated with different immune checkpoint modulators.



Biobanking & Data Management Platform

Goals Achieved in 2018

- ✓ Integration of additional databases into the DZL Data Warehouse
- ✓ Improvement of data quality through data harmonization (annotation, terminology, ontology)
- ✓ Creation and implementation of a Broad Informed Consent for children & young people (completion in 2019)
- ✓ Project planning and assignment using the central Data Warehouse
- ✓ Further development of interaction with the DZG

Goals for 2019

- Creation and implementation of a Broad Informed Consent for children & young people (see above)
- Prospective sampling of biospecimen and associated clinical data
- Integration of additional databases, cohorts, and registries into the DZL Data Warehouse; improvement of data depth and data quality
- Use of the DZL Data Warehouse as a service infrastructure (project planning, providing biomaterial and data)
- Implementation of additional features to increase functionality of the DZL Data Warehouse

The aim of the DZL Biobanking Platform is the SOP-based acquisition, processing, collection, and storage of biomaterial as well as the collection of associated clinical data from the most diverse pulmonary disease areas in compliance with all necessary legal standards. Both scientists within the DZL and external cooperation partners should be able to access biomaterial and data easily and in compliance with the rules. In terms of quality management, the harmonization of ethical and legal documents, data protection concepts, and standard operating procedures associated with quality control and data management is a key objective of all DZL sites.

Scientific Coordinators

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Administrative Coordinator

Dr. Jutta Schlegel (UGMLC)

Central Biobanking Management

Dr. Clemens Ruppert (UGMLC)

Central Data Management

Raphael Majeed (UGMLC)

Research Highlight 2018

CoMetaR – Collaborative Metadata Repository

Conducting meaningful clinical research requires sufficient numbers of patients who meet certain criteria. One lung research center alone often cannot provide these numbers, so patients from other centers must be involved. To establish this process comprehensively across the entire DZL, the central Data Warehouse has been set up, which includes information on patients of all participating sites and can thus provide larger patient cohorts. The data stored include, for example, diagnoses, available biomaterial, questionnaires, measurements, and previously applied therapies.

To integrate the data of the individual clinics into this large data pool, DZL researchers need to agree on a common catalog. They must find out jointly what information is of interest to various researchers and can also be delivered by various clinics. If a question the patient has been asked is very specific, there is a high probability that no other clinic will ask this question. If it is too general, it might not provide sufficient information. Besides the question as to what data are recorded, it is also necessary to clarify how to structure and annotate the information. The right structure allows the researchers to intuitively search the catalog. The annotation includes the designation, the unit of measurement, and a descriptive text, ensuring that every catalog user knows unambiguously what the parameters are about. In case of uncertainty, for example, it might happen that sepsis is accidentally recorded as cause of death instead of merely as a comorbidity. Data is also often provided with an internationally valid code.

With metadata, we refer to information that describe the data in the Data Warehouse. The annotations and the structure mentioned above are part of this metadata. To view and jointly edit the information, the DZL Biobanking & Data Management Platform has developed the Collaborative Metadata Repository (CoMetaR). A web page enables the scientists to search the metadata catalog and view all the information on the data stored. Many researchers from different DZL Disease Areas contributed their expertise during the creation and administration of the catalog.

Metadata management represents a challenge for the international research community. To enjoy the benefits provided by an increasingly networked world, the DZL adheres to globally established technological standards like RDF, Git, and SPARQL as well as to current principles of data organization such as the “FAIR Data Principles” (“Findable, Accessible, Interoperable, and Reusable”).

Further Information:

- ☑ Stöhr MR, Majeed RW, Günther A (2018) Using RDF and Git to Realize a Collaborative Metadata Repository. *Studies in health technology and informatics* 247:556-560
- ☑ Stöhr MR, Helm G, Majeed RW, Günther A (2017) CoMetaR: A Collaborative Metadata Repository for Biomedical Research Networks. *Studies in health technology and informatics* 245:1337.



Screenshots of the publicly available Collaborative Metadata Repository (CoMetaR) of the DZL Biobanking & Data Management Platform



Imaging Platform

DZL scientists have access to a wide range of innovative imaging approaches in microscopy and radiology to gain improved knowledge of the emergence and development of lung diseases, evaluate the efficacy of drugs, and support drug-discovery

Goals Achieved in 2018

- ✓ Continuation of the imaging technologies portfolio for prospective clinical studies
- ✓ Formation of a new working group to pursue the establishment of a Human Lung Atlas
- ✓ DZL Platform Imaging Workshop 2018 hosted by UGMLC – knowledge transfer of state-of-the-art imaging technologies
- ✓ First joint meeting of the DZL with the German Cancer Consortium (DKTK) on the subject of “Radiomics”

Goals for 2019

- Continuation of the imaging technologies portfolio for prospective clinical studies
- Development of imaging biomarkers for diagnosis and monitoring of pathological changes of the airways for ongoing clinical studies
- Human Lung Atlas – working program
- DZL Platform Imaging Workshop 2019 in Munich
- Facilitate closer links and transition from preclinical, translational and clinical imaging

processes. The Imaging Platform ensures the availability of different imaging technologies within the DZL and facilitates the use of imaging for research and translation. “Imaging” is understood as the interaction of imaging approaches of various modalities and with different resolutions and dimensions in the preclinical, translational, and clinical fields.

In 2018, the Imaging Platform set the course for the establishment of lung radiomics. Radiomics refers to the use of deep-learning tools to analyze the data of medical imaging (such as CT or MRI), allowing us to define new and complex imaging biomarkers. This opens up completely new approaches to pooling these imaging biomarkers with clinical, biological, and genomic data from clinical practice and sharing this information. On the one hand, this enables us to derive models and simulations; on the other hand, we can predict prognosis and outcomes in an interdisciplinary way. Radiomics and the development of the necessary algorithms and analysis programs are still in the early stages; in the future, however, they will make an important contribution to personalized medicine.

Scientific Coordinators

Prof. Dr. Peter König (ARC�)

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Administrative Coordinator

Dr. Birgit Teucher (TLRC)

First steps towards clinical synchrotron phase-contrast lung imaging in patients

The anatomical location of the lungs as well as breathing movements pose a challenge to intravital imaging for most imaging techniques. Although computer-tomography (CT), for example, is a well-established method for the detection of lung tumors, lung embolism or inflammatory and mostly chronic lung diseases, we need to develop even more advanced innovative technologies for the depiction of small lung structure.

One such innovative technology is high-resolution synchrotron-based phase-contrast imaging (PBI), which offers new possibilities for the characterization of anatomical structures in healthy and diseased lungs. In comparison to CT, phase-contrast tomography of the lungs has the advantage of producing images that are richer in contrast and plasticity. DZL radiologist from Heidelberg in collaboration with the Institute of Diagnostic and Interventional Radiology at the University of Göttingen, conducted a first proof-of-concept study (feasibility study) to demonstrate that synchrotron-based phase-contrast imaging of small regions within the lung can be further developed for later application in the clinical context. For this first battery of tests, six porcine lungs continuously ventilated by use of compressor were transported to the Elletra Synchrotron facility in Trieste for further investigation.

PBI achieved an approximate four times higher resolution (100µm) than commonly used clinical CT (400–600 µm) when scanning local areas of interest of 140 mm x 140 mm x 4 mm. The fact that small lung structures such as the interlobular septum (delicate strands of connective tissue separating primary lung segments) can be depicted in great detail with PBI is an important finding, as it greatly contributes to the pathological and radiological assessment of many pulmonary diseases. In another experiment PBI could successfully detect an artificially generated pulmonary nodule (small, roundish growth on the lung; image 2, while it was not possible to visualize the nodule in clinical CT (image 1). Important for the potential clinical application of PBI is the fact that for the experiments reported here only a fraction of the X-ray dose required for clinical high-resolution CT scans was used.

One limitation of the model presented is the low radiation density, which would not yet allow for the localization of a pulmonary nodule in the clinical setting.

For the generation of a virtual biopsy it is therefore necessary to first obtain a CT image of the chest to identify areas of interest. Once these have been identified we can use PBI to investigate further. In future, these virtual biopsies may help to reduce the number of invasive lung biopsies and thus the risk of complications.

For the technique to fulfill its potential as future application in the clinical setting, the challenge will be to develop a rotation unit that reduces time needed for image acquisition. In a next step, further developments are also warranted to control the influence of respiratory motion on image quality.

Further Information:

Wagner WL, Wuennemann F, Pacil  S, Albers J, Arfelli F, Dreossi D, Biederer J, Konietzke P, Stiller W, Wielp tz MO, Accardo A, Confalonieri M, Cova M, Lotz J, Alves F, Kauczor HU, Tromba G, Dullin C (2018) Towards synchrotron phase-contrast lung imaging in patients – a proof-of-concept study on porcine lungs in a human-scale chest phantom. *J Synchrotron Radiat* 25(Pt 6):1827–1832



Image 1: Clinical CT- imaging of the porcine lungs at the radiology unit of the university hospital "Ospedale di Cattinara" in Trieste.

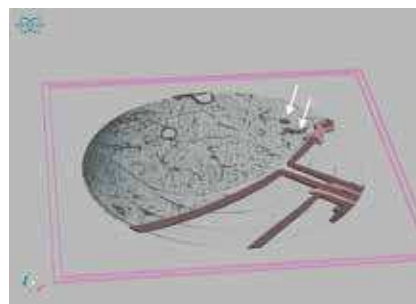


Image 2: Three-dimensional depiction of a local area of ventilated fresh porcine lung. White arrows indicate artificial lung nodules.

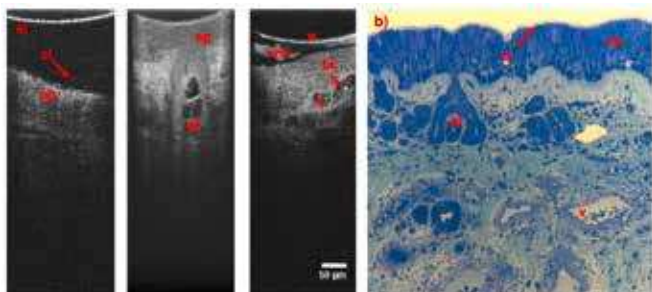
Research Highlight Microscopy 2018

New high-resolution method for the investigation of nasal mucosa

For many diseases, such as inflammatory and metabolic diseases or cancer, the histological assessment of tissue samples is necessary for the identification and characterization of the underlying pathological mechanisms. The burden and risk involved with obtaining tissue biopsies is clearly of disadvantage to patients. Also, once the biopsy has been obtained we cannot observe any dynamic biological processes associated with a living organism, such as the movement of the cilia (tiny, hair-like structures) of the airway epithelium. In contrast, the application of intravital microscopy (IVM) would offer us the opportunity to observe such phenomena in the living organism.

Cystic Fibrosis (CF) is a progressive, genetic disorder that affects mostly the lungs, but also the pancreas, and other organs. The defective gene responsible for CF leads to the creation of thick and sticky mucus that is a rich breeding ground for bacteria and promotes inflammation, which causes irreversible damage to the lung. Primary ciliary dyskinesia (PCD) is a rare genetic respiratory disease that affects the cilia that line the airways. Patients with PCD are prone to infections of the airways like bronchitis and pneumonia as well as chronic, recurring ear and sinus infections.

For these diseases, intravital microscopy of the airways offers the opportunity to investigate further the underlying pathological mechanisms of the dysregulation of mucus function and transport. This requires an endoscope that produces three-dimensional, high-definition images. Confocal laser microscopy, for example, produces dynamic high resolution images at the cellular level of tissues, such as the small intestine and colon or the esophagus and stomach. However, the images produced are only two-dimensional.



a) emOCT image of nasal mucosa. b) Histology of a corresponding sample. The resolution is sufficient for the depiction of cilia (ci), epithelium (ep), glands (gl) and vessels (v). Mucus is visible and mucus transport can be quantified.

Similar to ultrasound but using light instead of sound, optical coherence tomography (OCT) produces cross-sectional images at a resolution of under 10 μm . With mOCT (microscopic OCT) resolution is sufficient for intravital volumetric (three-dimensional) microscopy. One major disadvantage with this method is, however, the small axial visual field that is easily disrupted due to inevitable movement of people or animals in the awake state.

DZL scientists have now overcome this problem by developing an endomicroscopic OCT (emOCT) that combines high lateral resolution with increased depth of field to image dynamic processes at rates of up to 80 frames per second. This successful advancement in methodology allowed for *in-vivo* imaging of the structure of human nasal mucosa at cellular resolution and the measurement of mucus transport. The cross-sectional images from the imaged volumes show movement of the cilia, cellular structure of the epithelium, blood vessels and cells. The important parameter of the velocity of mucus transport could also be determined.

This new method for the imaging of nasal mucosa is an important advancement for diagnostic purposes as well as the monitoring of treatment of lung diseases. By measuring ciliary activity and mucus transport *in vivo* we gain a much better understanding of the effect of treatment on underlying pathological mechanisms. Further, the imaging of the nasal air passages is much less invasive and easier to conduct than a bronchoscopy of the lower airways. All that is needed to capture cilia and mucus as well as morphological and functional changes is an endoscope of 5 cm in length.

Further Information:

✉ Schulz-Hildebrandt H, Pieper M, Stehmar C, Ahrens M, Idel C, Wollenberg B, König P, Hüttmann G. Novel endoscope with increased depth of field for imaging human nasal tissue by microscopic optical coherence tomography (2018) Biomed Opt Express 9(2):636–647

DZL Technology Transfer Consortium

Chairman

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:





Clinical Trial Board and Clinical Studies in the DZL

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 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, there have been annual calls for proposals. 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 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, DZL investigators are 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.

Scientific Coordinators

Prof. Dr. Jürgen Behr (CPC-M)
Prof. Dr. Susanne Herold (UGMLC)
Prof. Dr. Norbert Krug (BREATH)
Prof. Dr. Michael Thomas (TLRC)
PD Dr. Henrik Watz (ARCN)

Administrative Coordinator

Dr. Annegret Zurawski (BREATH)

Investigator Initiated Trials supported with DZL Funds

Coordinator(s)/ scientist(s)	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	Pneumonia and Acute Lung Injury	BREATH, UGMLC	GM-CSF Inhalation to improve Host defense and Pulmonary barrier Resorption (GI-HOPE)
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
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
Reck M / Ammerpohl O / Barreto G	Lung Cancer	all	Monitoring of patients with NLCLC – epigenetic analysis of liquid biopsies and RNA-analysis in exhaled breath condensates
Schulz H / Meiners S / Vogelmeier C / Behr J	COPD	CPC-M, UGMLC	Proteasom Function as a Bio-Marker for COPD
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
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 DNAzyme solution SB010 in patients with moderate to severe COPD – A randomised, double-blind, parallel, multicentre, phase IIa pilot study
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 Collaborations, Partnerships, and Networks

In the German Center for Lung Research (DZL), more than 240 scientists and their work groups, currently from a total of 29 university and non-university research institutions as well as clinics at five DZL sites in Germany and other sites of associated partners, all work together. This means that an intensive exchange both between DZL researchers among the sites and of the entire network with external partners is of particular importance, all devoting themselves to one common goal: to research and combat lung disease to the best of their ability. Besides weekly telephone conferences and numerous regular meetings of the work groups, committees, and administrative units, particular attention should be brought to the Annual Meeting, for which all DZL members, including many junior researchers, get together to exchange views on the status of their projects.

Around 480 DZL scientists, physicians, and junior researchers got together for the **7th DZL Annual Meeting in Bad Nauheim on February 8 and 9, 2018** to exchange their views and experiences from current research projects. With highlight presentations, moderated poster sessions on around 290 submitted poster abstracts, numerous meetings of work groups, and a get-together on the first evening, the Annual Meeting provided excellent conditions for a networking scientific exchange. Seven members of the Advisory Board strongly supported the Board of Directors with advice on the further development of the Center. During the festive evening ceremony, DZL Chairman Werner Seeger officially welcomed **Hans-Ulrich Kauczor as a new DZL Board member** and Director of the Heidelberg site. At the same time, he thanked the **former Board member** and site spokesman **Marcus A. Mall** for his great long-time commitment to the DZL. In early February 2018, Markus Mall assumed his Professorship for Pediatric Pulmonology and Immunology at Charité – Universitätsmedizin Berlin; however, he will maintain close ties with the DZL through cooperation projects over the Berlin Institute of Health (BIH) newly associated with the DZL.

From **April 12 to 14, 2018**, the DZL organized the **6th International DZL Symposium**, themed “Exacerbations of Chronic Lung Disease”, in conjunction and collaboration with the 5th Munich Lung Conference (MLC) hosted by the Helmholtz Center. The conference theme of acute exacerbation (worsening) of chronic lung disease often caused by infections is of great

interest all over the world and is also given special attention at the DZL. In this respect, the exchange on both disease-specific and comprehensive diagnostic options, as well as the discussion of pathophysiological concepts play a particularly important role for future clinical care. Presentations from the Disease Areas of Pulmonary Fibrosis, Asthma and Allergy, and Acute Lung Injury examined the overall theme of exacerbation from different perspectives.

On top of that, numerous other events with DZL involvement took place at the DZL sites.

Since its foundation, the German Center for Lung Research has been part of several networks conducting research into various pulmonary diseases, while it is associated with other organizations contributing to the realization of research projects. The expansion and development of **partnerships in the fields of science and research, promotion of junior scientists, patient information and interests, clinical studies, industry, and educational work** continue to be actively pursued. Numerous **national and international collaborations** 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 clinical practice about pulmonary diseases. The scientists and doctors at the DZL sites take on an advisory role for editorial contributions of the LIS and individual patient inquiries sent to the LIS. In addition to its online platform, the Lung Information Service also organizes events such as patient fora on special subjects. In 2018, patient fora were organized in collaboration with the DZL at various sites of the Center.

For instance, jointly with the LIS, the German Lung Day (Deutscher Lungentag), and the Carl Gustav Carus University Hospital in Dresden, the DZL invited interested patients and their families to the **Patient Lung Forum on March 17, 2018 in Dresden**, the capital city of the German state of Saxony. The theme of the event attended by over 100 people was “Chronic Lung Disease: Prevention and Treatment, Research and Cure”. Besides lung diseases in childhood and youth, the



forum addressed current treatment options for Asthma and COPD as well as disease prevention. For one afternoon, proven experts outlined the current state of knowledge in short presentations. Furthermore, the participants had the opportunity to hold in-depth discussions with the speakers and obtain information at the booths of self-help organizations, the LIS, the German Lung Day, and the DZL as well as exchange views and experiences with other patients.

Since September 2016, the DZL and the LIS have also been offering patients, their families, and interested members of the general public an **overview of clinical studies currently carried out by DZL researchers**. The internet-based list on the LIS website sets out the objectives, admission criteria, duration, and investigation/treatment methods of each study in a way that is easily understandable. Using this service, interested patients may contact the study sites directly, which facilitates access to clinical studies. This new list of studies is updated and extended on a regular basis.

Following the request to focus more strongly on patient interests, the DZL invited **representatives of patient organizations** to a **Round Table** for the third time. The event took place on **March 16, 2018** on the margins of the DGP Congress in Dresden. Scientists of the various Disease Areas investigated and treated at the DZL provided a current overview of various topics and created the opportunity to exchange information and discuss matters of common interest again during the round-table session.

Particularly pleasant and important for strengthening the representation of patient interests within the DZL is the contribution of **Dr. Pippa Powell**, Manager of the European Lung Foundation (ELF), as a member of the Scientific Advisory Board of the DZL. Founded by the European Respiratory Society (ERS), ELF aims to bring together patients, the general public, and pulmonary professionals to make a positive contribution to respiratory medicine.

A success arising directly from this collaboration is the publication of the German translation of the **European Patient Ambassador Programme (EPAP)**. This free online program has been developed for patients, their families, and carers. The course enables them to expand their skills in obtaining infor-

mation and interacting with medical staff, political decision-makers, researchers, and the media. The program is suitable for patients with any kinds of diseases. It has been developed by ELF; besides English, French, Italian and Dutch, it is now also available in German.

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. In the German-wide register for the pulmonary disease COPD, the fourth most common global cause of death, 31 study centers are involved. The cohort study COSYCONET involves long-term observation of more than 2,700 COPD patients. The investigations are to 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 database, and phenotypic data, which serve as a basis for various subprojects. COSYCONET has been integrated into the DZL as an associated partner since 2016.

Since the beginning of 2013, **CAPNETZ (German Competence Network for Community Acquired Pneumonia)** has been an associated partner of the DZL. The Competence Network has set itself the goal of acquiring new information related to the origin and the course of Community-Acquired Pneumonia (CAP), developing improved diagnostic standards and therapies, and strengthening methods of clarification and prevention. CAP is still a potentially life-threatening disease and the sixth most common cause of death in Germany. With the largest Europe-wide comprehensive epidemiological study comprising over 10,000 CAP patients and the most extensive CAP database in the world, the DZL has gained a strong partner in this field. The DZL has 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), a program funded by the European Union to carry out research into infectious diseases with epidemic potential.

Registries and patient cohorts are of great and increasing importance to translational research carried out by the DZL. Large cohorts and registries are brought into the DZL by associated institutions. For instance, together with CAPNETZ, the DZL has since 2015 been involved in the establishment

of the bronchiectasis registry **PROGNOSIS (The Prospective German Non-CF-Bronchiectasis Registry)** and the pediatric CAP cohort **Ped-CAPNETZ**. PROGNOSIS is also part of the EU-funded European registry **EMBARC (European Multicentre Bronchiectasis Audit and Research Collaboration)** and has been an associated partner of the DZL since the turn of the year 2016/17. DZL scientists are also actively involved in many other registries and cohorts, e.g. in the pulmonary hypertension registry **COMPERA (Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension)** or in the **German National Cohort (NAKO)**.

Initiated in 2014, the **German National Cohort (NAKO)** is to date the largest German population study to carry out research into widespread diseases. The DZL has been connected with the German National Cohort from the beginning 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 lung disease as well as other research projects are pursued.

The long-standing cooperation of DZL researchers with **PROGRESS (Pneumonia Research Network on Genetic Resistance and Susceptibility for the Evolution of Severe Sepsis)** was formalized at the turn of the year 2016/17 with the admission of the network as an associated partner. Research is carried out on the genetic basis for disease pathogenesis and the resistance to community-acquired pneumonia. The focus of this research is on the question as to what factors influence whether pneumonia will take an uncomplicated or a difficult course, including progression to 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 lungs. Cohort projects in the field of COPD and bronchial asthma are carried out, while phase I-IV clinical studies in the field of respiratory medicine with a focus on COPD, bronchial asthma, and other more rare disorders are conducted. The long-standing close cooperation with the LungenClinic Grosshansdorf and the DZL has since then been intensified through this new partnership.

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 both non-communicable and communicable pulmonary diseases. An associated partnership with the RKI was finalized in March 2017. This allows strengthening the DZL expertise 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, and Lung Cancer. On top of that, a cooperation is envisaged in various pilot projects related to infectious diseases.

Furthermore, an associated partnership of the **Berlin Institute of Health (BIH)** was initiated in 2017 and formally agreed upon in March 2018. For instance, this cooperation involves partnership projects on translational lung research in the Cystic Fibrosis Disease Area. Further collaborations are pursued in the Disease Areas of Pulmonary Hypertension, Pneumonia and Acute Lung Injury, and Asthma and Allergy.

From the beginning, the **German Respiratory Society (DGP)** has been an important strategic partner of the DZL. Collaborations, e.g. in the field of promoting young pulmonary scientists and doctors as well as in the exchange with patient organizations, will continue to be strengthened. What is more, the DZL regularly publishes its **“Mitteilungsseiten”** (announcement pages) in **“Pneumologie”**, the official journal of the DGP, the DZL, and the DZK (German Central Committee against Tuberculosis). At the DGP Annual Meeting, the German Center for Lung Research is regularly represented with an information desk and presentations. Members of the DZL Board and DZL scientists have also held and continue to hold significant positions within the DGP, thereby contributing to the promotion of joint activities. For instance, DZL Board member Prof. Dr. Klaus F. Rabe (Grosshansdorf/Kiel) was until March 2019 President of the DGP.

The **German Society for Pediatric Pneumology e. V. (GPP)** promotes research, networking, and the exchange of information among 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 organizes scientific symposia

and workshops on a regular basis, while integrating research content of the DZL. DZL researchers also hold key positions within the GPP and are greatly involved in the scientific work groups of the society. In April 2018, DZL researcher and physician Prof. Michael Kopp was elected President of the German Society for Pediatric Pneumology (GPP), ensuring a high level of exchange between the GPP and the DZL.

Since 2013, the DZL has been a full member of the **Technology, Methods, and Infrastructure for Networked Medical Research (TMF)**, the umbrella organization for networked medical research in Germany. Particularly in the fields of biobanking and establishing central data management, the DZL cooperates closely with the TMF. Especially the field of biobanking draws on the regular and intensive exchange with biobanking and IT representatives from the German Centers for Health Research and the German Biobank Node (GBN).

The DZL also supports various **anti-smoking campaigns**, among them the **Education against Tobacco (AGT)** initiative, which focuses on young people. Each year, medical students from around 30 faculties in Germany, Austria, and Switzerland inform approximately 20,000 students from grades 6 to 8 on a voluntary basis about the dangers of smoking tobacco, campaigning for smoke-free classes. The project involves not only students but also teachers, doctors, and professors. The DZL Chairman and other DZL researchers are members of the Scientific Advisory Board of the initiative. In both 2014 and 2017, the initiative had already been honored with the **Federal Prize by the German Chancellor within the framework of the “startsocial” competition** for outstanding voluntary projects in Germany. In 2018, the initiative received the **EU Health Award** by the European Commission.

Together with the other **German Centers for Health Research (DZG)**, the DZL is part of a German-wide network in medical research. The DZG benefit from the regular exchange of information on joint strategic, infrastructural, and scientific subjects on many different work levels. For the benefit of the patient, synergistic effects can thus be used and created where, for instance, topics in pulmonary, cancer, infection, or cardiovascular research overlap, as is the case with the Disease Areas of Lung Cancer, COPD, Pneumonia, or Pulmonary Hypertension. A joint objective of the DZG is their continued

presence to inform decision-makers and the general public. The DZG centers were thus represented again with scientific symposia and a common booth at the **Annual Meeting of the German Society of Internal Medicine (DGIM)**, which took place from **May 4 to 7, 2018**. At the DZL symposium, proven DZL experts summarized the current state on the subject of “Personalized Therapies for Lung Diseases of Today and Tomorrow” for the clinical pictures of Asthma, Pneumonia, Pulmonary Hypertension, and Lung Cancer. Furthermore, the DZL was represented jointly with four of overall six DZG centers at the **18th Annual GAIN (German Academic International Network) Conference in Boston, United States**, which took place from **September 7 to 9, 2018**. The conference is aimed at German junior researchers who are currently working in facilities in the United States and Canada and consider returning to Germany. At the Talent Fair, more than 400 participants obtained information on the offerings of the exhibiting German research institutions and universities. In addition to their information desk, the DZG provided an extensive overview of the structures, research activities, and strategies of the centers in their **workshop on “New Career Paths in Clinical and Translational Research”**. Interested junior researchers benefit from the collaboration across the DZL institutions and the excellent shared infrastructures. The coherent approach results in long-term perspectives.

The **European Respiratory Society (ERS)**, one of the largest and most significant societies in the field of respiratory medicine, is an important partner of the DZL. This close association is marked, for example, by the appointment of Prof. Dr. Tobias Welte as President of the ERS for the 2018/19 term of office or the chairing of 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 desk and presentations by DZL scientists, as was also the case in 2018 in Paris. The ERS Congress is the largest meeting of respiratory researchers and clinicians in the world.

DZL physicians are committed to finding ideal diagnostic and therapeutic approaches to lung diseases by contributing to keep **treatment guidelines** up to date. In 2018, the DZL was involved in publishing the **Guideline on Nosocomial Pneumonia**, the **Updated Guideline on Lung Cancer**,

the **Updated Treatment Recommendation on Metastatic Non-Small-Cell Lung Cancer**, and the **Revised Guideline on COPD**. Medical guidelines are aimed to assist physicians in the treatment of their patients. They represent the current state of substantiated research findings, providing an important interface between science and medical practice.

In addition, further numerous strategic partnerships of the individual DZL sites have been set up with **international scientific and economic partners**. The expertise in industrial contacts is strengthened by the contribution of **Prof. Dr. Stephen Rennard**, member of the International Scientific Advisory Board of the DZL.

DZL scientists are currently cooperating with well over 100 international economic partners, especially within the framework of projects on basic research and applied research as well as in the conduct of clinical studies. These particularly registration-oriented clinical studies are conducted and supported by partners such as AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly and Company, GlaxoSmithKline, Hoffmann-La Roche or Novartis/Novartis Pharmaceuticals.



DZL Academy: Enabling Early Career Scientists

A vibrant early career scientist community is a key asset for meeting today's and future challenges of respiratory medicine and creating a strong base for innovation in lung research.

The DZL Academy promotes the career development of students, doctoral candidates, and post-doctoral researchers of medicine and the life sciences relating to clinical, translational, and basic lung research. The Academy provides funding for courses and conferences as well as flexible funds for research

exchange. Moreover, we offer attractive research positions for excellent national and international early career scientists. The DZL Academy is also dedicated to supporting early career scientists in taking advantage of family-friendly programs and infrastructures at the various DZL sites.

The DZL Mentoring Program "Careers in Respiratory Medicine" strives to provide a supportive environment for Fellows to develop their personal growth and career development plan. To date, 24 early career scientists have benefited from the program; it allows mentees to shape their individual profile under the guidance of experienced mentors, supported by courses in management, leadership, and soft skills. In 2018, the Academy focused on laying the foundations for turning the mentoring program into a rolling program that is more attuned to mastering work-life balance in the modern research environment.

In addition to the wide range of site-specific graduate programs and other career-development opportunities on offer (please refer to the DZL Academy homepage for a full listing), the DZL Academy aims to strengthen the early career scientist's sense of belonging to the DZL community by providing a supportive environment for the establishment of a strong peer network within and beyond the DZL.

Goals Achieved in 2018

- ✓ Joint consultation paper on "Career and education in translational research" of all German Centers for Health Research
- ✓ Funding of DZG/DZL Academy training courses and mobility grants
- ✓ Survey conducted among DZL Fellows regarding their training and career-development needs

Goals for 2019

- Election of Fellow Representatives to the DZL Academy Board
- Organization of the 1st DZL Academy Fellow Symposium
- Restart of the DZL Mentoring Program
- Funding of mobility grants and training courses
- Concerted activities with other German DZG centers
- Extension of the portfolio of DZL Academy activities to foster DZL-wide research activities driven by early career scientists

DZL Academy Board



Antje Brand



Jörn Bullwinkel



Doreen Franke



Michael Kreuter



Silke Meiners



Rory E. Morty



Birgit Teucher



Annegret Zurawski

The DZL Academy Board is made up of members of all five DZL sites. It is dedicated to conceptual and strategic planning as well as to the implementation of programs and promotional opportunities. It supports the DZL Board in the selection process for all tenders and prepares recommendations on the allocation of funds.

Highlights 2018

Membership Increased to over 300 Academy Fellows

We are very happy to report the increase of the DZL Academy Fellow Community to >300 Fellows in 2018. Female membership is currently in the lead with 55% (Figure 1). The majority of Fellows are doctoral students (postgraduates), followed by postdocs and graduate students (Figure 2). The split between the disciplines of medical and biological sciences is currently at 36% versus 64% (Figure 3). International students make up 37% of the Fellow Community, which reflects our competitiveness in attracting researchers from all over the world.

Gender

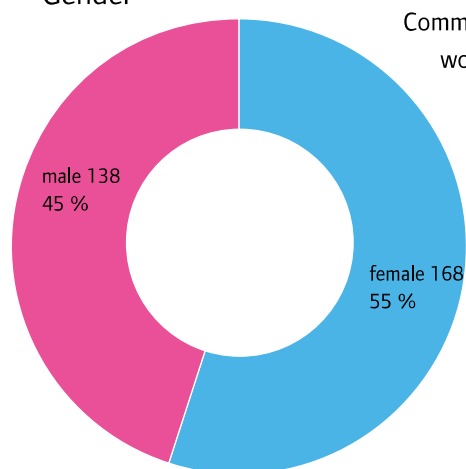


Figure 1

Education Level of Fellows

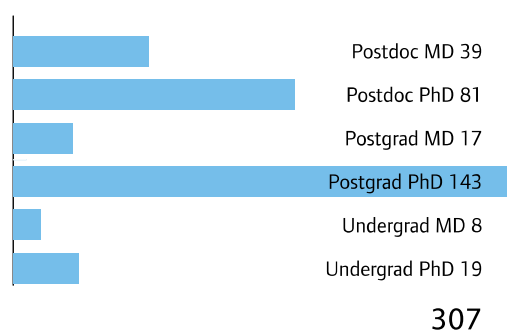
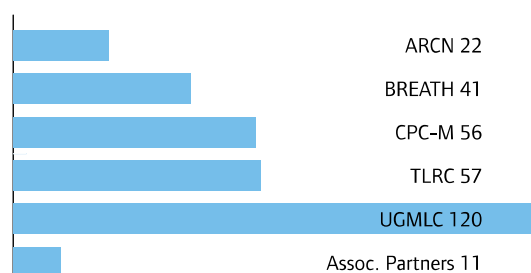


Figure 2

Fellows per DZL Site



Disciplines

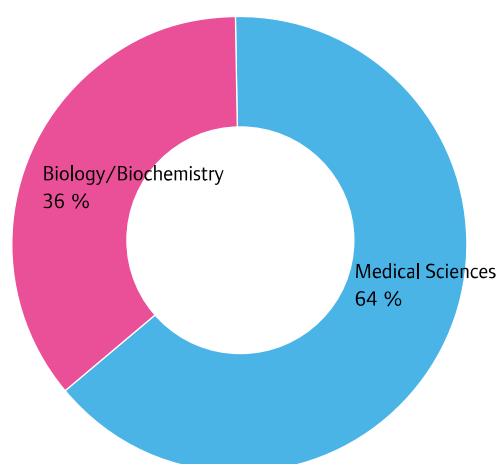


Figure 3

Nationality

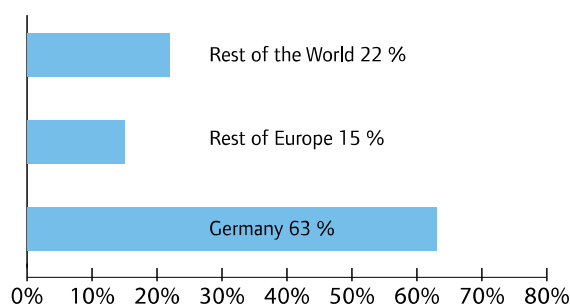


Figure 4

Munich International Autumn School for Respiratory Medicine 2018

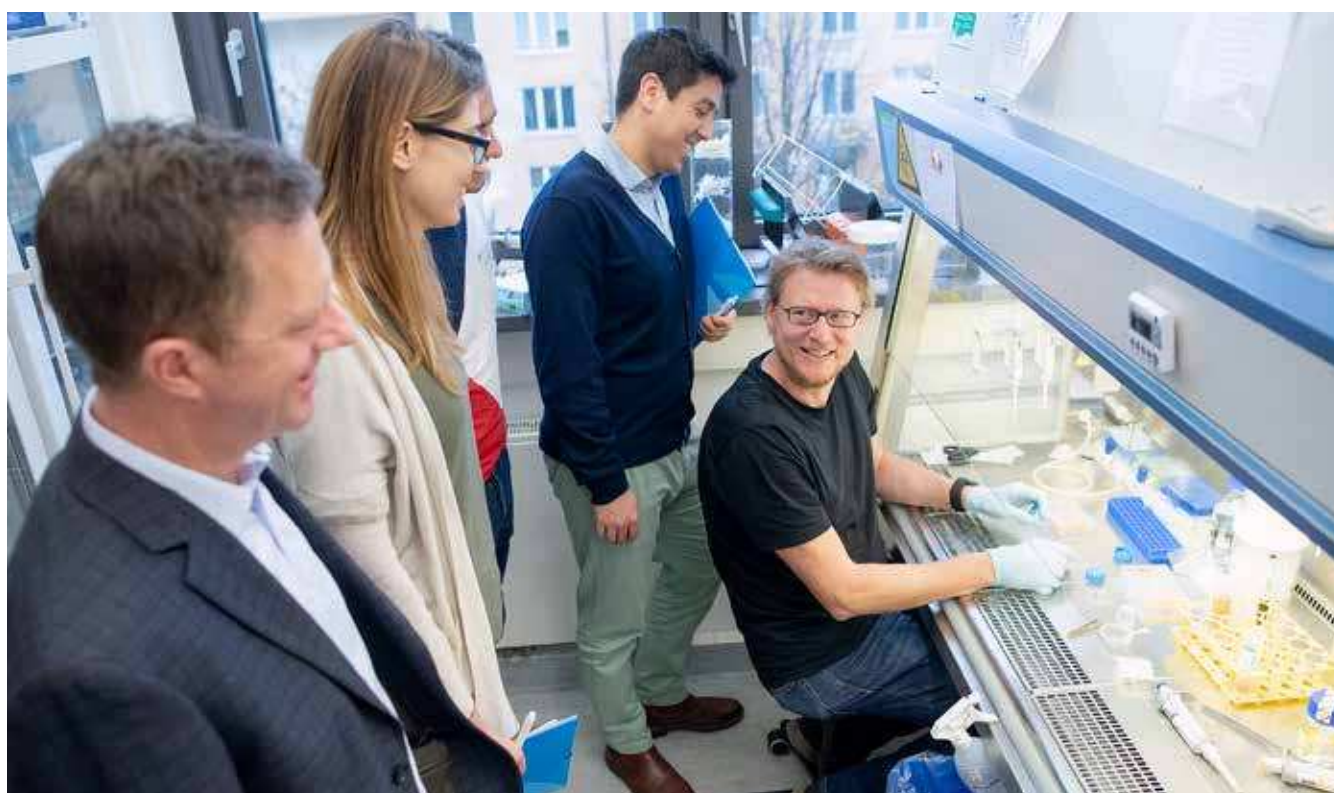
With increasing numbers of patients suffering from lung diseases worldwide, there is an urgent need for novel therapeutic and diagnostic strategies. Respiratory research is therefore indispensable and must be visionary and translational.

From all over the world, about 15 highly motivated early career scientists from the natural sciences and medical field had been selected to join the 6th Munich International Autumn School (MIAS) for Respiratory Medicine in November 2018. The event was organized by the CPC Research School at the Comprehensive Pneumology Center (CPC), with financial support from the Stiftung AtemWeg and Boehringer Ingelheim.

The conceptual idea of MIAS is to provide a platform for clinical and basic research scientists to foster scientific exchange with each other and renowned scientists in the field, in particular with regard to translational research ideas. The exchange is facilitated by hands-on practical training modules both in laboratory and clinical settings as well as by networking sessions.

The one-week program started with an interactive poster session, where participants showcased their research interests and current findings to establish a basis for networking among MIAS participants, MIAS lecturers, and CPC researchers. During the course of the week, participants were assigned to various experimental training modules with a special focus on standard and novel technologies for modern respiratory research, including (primary) cell culture and animal models, flow cytometry, biotechnological and imaging applications, and single-cell RNA sequencing. The participants gained detailed insights into the importance of translating scientific findings into clinical practice when they visited different hospitals in and around Munich (LMU University Hospital system and the Asklepios Specialist Clinic for Pulmonary Diseases in Munich-Gauting).

The MIAS curriculum included various lectures by renowned scientists on novel findings and technologies to inspire outside-the-box thinking in early career scientists and clinicians. Interactive lunch sessions and regular coffee breaks were used to interact with the speakers and get specific questions answered.



German-French Lung Retreat in Paris, France in September 2018

Prior to the Annual European Respiratory Society (ERS) International Congress, MD and PhD students as well as postdocs from the German-French Lung School met for a two-day-retreat in Paris to discuss “hot” lung topics as well as to extend and foster their multilateral networks.

The German-French Lung School was founded in 2013 as a cooperation between the German Center for Lung Research (DZL) and the French Institut national de la santé et de la recherche médicale (Inserm) with the aim of promoting early career scientists to contribute new impetus to international lung research. All German-French Lung Schools have been organized by a team from both countries.

Early career scientists presented and discussed their own scientific work in talks as well as in two poster sessions and ‘conversation walks’, addressing a plethora of topics in respiratory research: Pulmonary Hypertension, Lung Fibrosis, Asthma & Allergy, Environmental Challenges for the Lung, Lung Cancer, and Novel Technologies in Experimental Lung Research and Bioengineering. A keynote lecture was given by Bradley Maron from the Brigham and Women’s Hospital in Boston.

The conference concluded with an informal career-mentoring session and a panel discussion by renowned international scientists on important aspects of professional choices and shared advice on career decisions. As unique as the personal stories of each person were, they jointly agreed on one message: Follow your aptitude and be passionate about what you do.



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.

Mitteilungen des DZL

Mitteilungsseiten des Deutschen Zentrums für Lungenforschung

Mit dem 7. DZL-Jahrestreffen, dem größten und wichtigsten internen Forum, startete das DZL in das Jahr 2018. Es folgten die Präsenz beim DGP-Kongress in Dresden mit zahlreichen Preisträgern aus den eigenen Reihen und die 5th Munich Lung Conference – zugleich Internationales DZL-Symposium. Da das DZL Belange von Patienten verstärkt in den Fokus rückt, möchten wir in dieser Ausgabe insbesondere auf den Online-Kurs für Patienten „EPAP“ hinweisen – der nun mit Hilfe des DZL und der DGP auf Deutsch verfügbar ist. In der Reihe „Klinische Studien im DZL“ stellen wir mit „ERT-BC und mit „EMoLung“ zwei Studien aus dem Krankheitsbereich Lungenkrebs vor.

(sb)

DZL beim 59. DGP-Kongress in Dresden

Vom 14. – 17. März 2018 präsentierte sich das DZL mit einem Informationsstand beim 59. Kongress der Deutschen Gesellschaft für Pneumologie und Beatmungsmedizin e.V. (DGP) in Dresden. Mehr als 3000 Teilnehmer kamen bei der größten wissenschaftlichen Veranstaltung im Bereich der Pneumologie im deutschsprachigen Raum zusammen, die in diesem Jahr unter dem Motto „Prisma der Inneren Medizin“ stand. Zahlreiche DZL-Vertreter hielten Vorträge zu ihren Fachgebieten, darunter Prof. Dr. Klaus F. Rabe, derzeitiger DGP-Präsident und DZL-Vorstandsmitglied. Viele der im Rahmen des Kongresses verliehenen Preise gingen erneut an Forscher aus den Reihen des DZL (siehe auch unter „DZL-Preisträger“). Bereits zum dritten Mal lud das DZL am 16. März 2018 Vertreter von Patientenorganisationen zu einem Runden Tisch ein. Wissenschaftler der verschiedenen

in DZL erforschten und behandelten Krankheitsbereiche gaben aktuelle Überblicke und boten im Zuge des Runden Tisches Gelegenheit zum offenen Interessensaustausch.

(sb)

Patienten im Fokus

Patientenforum „Die chronisch kranke Lunge – Vorbeugen und behandeln, forschen und heilen“ in Dresden

Im Anschluss an den DGP-Kongress veranstalteten das DZL und der Lungeninformationsdienst (LID) in Kooperation mit dem Deutschen Lungentag und dem Dresdner Universitätsklinikum Carl Gustav Carus am 17. März 2018 erstmals ein „Patientenforum Lunge“ in der sächsischen Landeshauptstadt. Die von mehr als 100 Teilnehmern besuchte Veranstaltung stand unter dem Motto „Die chronisch kranke Lunge – Vorbeugen und behandeln, forschen und heilen“. Neben Mukoviszidose und Lungenerkrankungen in Kindheit sowie Jugend ging es auch um aktuelle Therapieoptionen bei Asthma sowie COPD und um das Thema Prävention. Den Auftakt machte DZL-Vorstandsmitglied Prof. Dr. Tobias Welte (Medizinische Hochschule Hannover) mit seinem Vortrag „Vorbeugen und Leben mit der Krankheit“. Im Zentrum standen die verschiedenen Impfungen, die für Menschen mit chronischen Krankheiten wie Asthma oder COPD empfohlen werden. Dr. Kristina Stamos (Kinder- und Jugendklinik

DGP-Präsident K. F. Rabe besucht den DZL-Stand (v.l. n. r.: S. Baumgarten, K. F. Rabe, A. Zurawski, C. Kalberlah, J. Bullwinkel, A. Hoesel, Foto: Mike Auerbach/DGP).

Verantwortlich: Sabine Baumgarten (Red.leitung), Dr. Jörn Bullwinkel (Co-Lektorat), Dr. Claudia Davenport, Franziska Hauptkorn, Dr. BirgitzFée

396 Mitteilungen des DZL, Pneumologie 2018; 72: 396-401

In the field of public relations, the DZL is involved with its own scientific symposia, its presence at national and international conferences, printed information such as brochures, flyers, and Annual Reports, its web presence (www.dzl.de), a newsletter as well as joint activities with the German Lung Information Service (LIS), including events organized for patients.

Several times a year, as again in 2018, the DZL also publishes the latest research results, event information, new appointments, and other news about the Center on its **“Mitteilungsseiten”** (announcement pages) in the scientific journal **Pneumologie**.

With numerous news items about DZL lung research and a great deal of information on the background and the structure

of the DZL, the range of information offered in 2018 could again be expanded further on the DZL website. The special homepage section **“Publications”** shows the latest publications by DZL researchers on a weekly basis. The research association also introduces itself in a short film portrait, which can be found on the DZL website as well as on YouTube.

In 2018, the comprehensive **DZL Annual Report 2017** was published again in both English and German. Alongside the achievements and highlights of the year 2017, the report presents the numerous successes of the DZL since its founding. Furthermore, diverse papers by and with DZL researchers were published in specialist journals and press reports.

Scientific Conferences and DZL Annual Meeting

In 2018, the DZL was represented at many large conferences. With an information desk and numerous award winners and presentations by its own scientists, the DZL played a highly visible role at the **59th Congress of the German Respiratory Society (DGP)** in March 2018 in Dresden. The DGP Congress represents the largest scientific forum in the field of respiratory medicine in the German-speaking world.

At the **18th GAIN Conference**, which took place in September 2018 in Boston, USA, interested junior researchers working in the United States had the opportunity to gain information on the career paths offered by the DZG and get in touch with relevant DZG stakeholders in a workshop organized by all DZG centers and at a joint DZG information desk.

At the **ERS (European Respiratory Society) International Congress** in Paris in September 2018, the DZL was also present with award winners, speakers, and session chairs. In the “World Village” Congress Area, together with other professional associations from all over the world, the DZL provided information about its activities and welcomed the ERS (Past) President, Professor Mina Gaga, to its booth. As part of the congress, DZL board member Prof. Tobias Welte took over the presidency of the ERS. The DZL’s presence at the largest congress in the world on respiratory medicine with more than 22,000 participants from 130 countries worldwide plays a vital

role in making the DZL more visible, both nationally and internationally.

In 2018, the DZL also attended numerous other meetings and scientific conferences contributing presentations and scientific expertise, for example at the **Retreat of the German-french Lung school** on the sidelines of the ERS congress in Paris. Under the motto “Exacerbations of chronic lung diseases”, the DZL organized the **6th International DZL Symposium in Munich** from April 12 to 14, 2018, in conjunction with the 5th Munich Lung Conference (MLC) hosted by the Helmholtz Zentrum.

Even in times of modern media, the personal exchange between scientists and the numerous DZL partner institutions from different German sites remains essential. The most im-

portant and largest meeting is the DZL Annual Meeting, which takes place alternately at all sites of the Center. On February 8 and 9, 2018, about 480 scientists, clinicians, and junior scientists discussed their project results, strategies and research objectives at the **7th DZL Annual Meeting in Bad Nauheim**. The work groups of the Disease Areas and Platforms also used the opportunity to exchange opinions and benefit from intensive consultation.

Focus on Patients

Strategically, the DZL is moving the concerns and interests of the patients increasingly into focus. Ever since the DZL was founded, the **Lung Information Service (LIS)** has been a professional and reliable partner for direct and understandable



DZL at the European Respiratory Society Congress 2019 in Paris

patient information. During the year, the DZL and the LIS organized three fora specifically for patients and their families at the DZL sites, each with more than 100 participants:

- March 17, 2018 (Dresden): 19th Patient Lung Forum on “Cystic Fibrosis and Lung Diseases in childhood and adolescence” as part of the DGP 2018 Annual Meeting
- April 7, 2018 (Hannover): 4th patient seminar on “Pulmonary Fibrosis” at Hannover Medical School
- June 2nd, 2018 (Hannover): 1st patient seminar on “Alpha-1-Antitrypsin deficiency” at Hannover Medical School

Another important part of the contact established with patients (or representatives) are the **DZL round-table discussions** held since 2016, enabling direct exchange on common concerns in the field of lung research. Furthermore, particularly important for strengthening the representation of patient interests within the DZL is the contribution of **Dr. Pippa Powell**, Manager of the European Lung Foundation (ELF), as a member of the Scientific Advisory Board of the DZL. Ever since the foundation of the European Respiratory Society (ERS), ELF aims to bring together patients, the general public, and pulmonary professionals to make a positive contribution to respiratory medicine. A success arising directly from this collaboration is the publication of the German translation of the **European Patient Ambassador Programme (EPAP)**. This free online program has been developed for patients, their families, and carers. The course enables them to expand their skills in obtaining information and interacting with medical staff, political decision-makers, researchers, and the media. The program is suitable for patients with any kinds of diseases. It has been developed by ELF; besides English, French, Italian and Dutch, it is now also available in German.

Lung Information Service

The Lung Information Service (LIS), based at the Helmholtz Center in Munich, is an important professional and reliable partner of the DZL to inform patients. The LIS shares knowledge directly from research to improve human health and strengthen health literacy. People affected by lung diseases

receive support to help them deal with their complex chronic conditions. The Lung Information Service provides access to

science, assisting patients in assuming responsibility for the management of their disease. The aim is to provide patients and the interested public with scientifically proven, up-to-date, and independent information. On average, 130,000 people visit the LIS website each month to gather information. The LIS has repeatedly received positive feedback regarding the quality and independence of the information provided.

Information is mainly shared in three different ways: via a comprehensive online portal, through patient events, and with publications (“Fact Sheets: The Most Important Information in Brief”).

At www.lungeninformationsdienst.de, the LIS provides both basic knowledge and new research results to patients, their families, and the interested public in an easily understandable manner. Since September 2016, the LIS has also integrated a platform on current clinical studies into the portal. Interested members of the public can obtain information on the objectives, admission criteria, duration, and investigation/treatment methods of each study, set out in a way that is easily understandable. Using this service, patients may contact the study sites directly, which facilitates access to clinical studies. The list is updated and expanded on a regular basis. By the end of 2018, 114 studies had already been recorded on the platform. Online Portal Key Topics of the Lung Information Service in 2018 were: Finally Smoke-Free (January), Lung Exercise (February), Tuberculosis (March), Transplantation (April), Pulmonary Hypertension (May), Epigenetics (June), Sarcoidosis (July), Lung and Respiration (August), Pulmonary Fibrosis (September), Biobanks (October), Vaccination (November), Clinical Studies (December).



From 2011 to 2018, the Lung Information Service published more than 800 news articles on its website. The main basis for the news published twice a week are publications on patient-relevant subjects in well-known scientific journals.

Alongside these purely scientific contents, the online portal also informs patients on recent topics, such as patient-relevant events, recommendations on recently published patient literature, or announcements of interesting TV or radio reports. Furthermore, the LIS sends out a monthly newsletter. Since 2016, the Lung Information Service has also been active on social media. It has its own Facebook profile with 2,580 subscribers and publishes new research information several times per week via the news service Twitter, where it now has 425



Lung Convention in Worms

followers. In 2018, the Lung Information Service published a new fact sheet on “Cystic Fibrosis” and reissued 10 fact sheets on “Asthma”, “Breathing Techniques”, “Diagnostic Imaging Techniques”, “Bronchiectasis”, “COPD”, “Inhalation” and “Lung Function”, “Pulmonary Fibrosis”, “Lung Exercise”, and “Pulmonary Hypertension”.

The information provided by the Lung Information Service is often picked up on by daily newspapers and other media. In 2017, for example, articles were published in the Berliner Morgenpost, the Westfalenpost, and journalMED. Since the summer of 2018, the LIS has also been publishing selected news in the journal Patientenbibliothek COPD in Deutschland (Patient Library COPD in Germany) [circulation of 30,000] in its own category “Lungenforschung aktuell” (Current Lung Research).

Perspectives

The Lung Information Service intends to offer additional services in the future to reach mainly people from educationally disadvantaged backgrounds more effectively. These might be explanatory videos or podcasts, which will then be distributed over various social-media channels. To strengthen the health literacy of people from migrant backgrounds, the services of the LIS could also be provided in other languages (Turkish, Russian, etc.) in the future.



DZL Highlights in 2018

More Informationen can be found at www.dzl.de

JANUARY

New Therapeutic Approach for the Treatment of COPD

DZL researchers find new drug candidates for the treatment of Chronic Obstructive Pulmonary Disease (COPD), a currently incurable condition.

MARCH

BIH Becomes New Associated Partner of the DZL

The cooperation with the Berlin Institute of Health involves, for example, partnership projects on translational lung research in the Cystic Fibrosis Disease Area.

FEBRUARY

New DZL Board Member

At the 7th Annual Meeting, Spokesman Prof. Dr. Seeger officially welcomes the Heidelberg-based scientist Prof. Dr. Hans-Ulrich Kauczor as a new DZL Board Member at the TLRC Site.

APRIL

Minister-President of Hesse Visits DZL

During the Zukunftswochen ("Future Weeks") organized by the state government of Hesse, Minister-President Volker Bouffier visits the DZL site Bad Nauheim.

MAY

Pioneering Work for the Heart and Lungs

DZL researchers discover a new promising therapeutic approach to the treatment of pulmonary hypertension and right heart failure.

JUNE

DZL Researcher Receives Marie Curie Fellowship

The postdoctoral researcher Sabine Bartel receives the fellowship of 150,000 euros for carrying out a two-year research project in the Netherlands. ▶

DZL



JULY**Lung Disease As a Result of Diabetes**

Researchers of the DZL and the German Center for Diabetes Research (DZD) find indications of the fact that shortness of breath and restrictive lung disease might be a late complication of type-2 diabetes.

AUGUST**Mechanism of Fibrosis Development Revealed**

DZL researchers reveal the mechanisms of the previously unexplained emergence of the incurable lung disease.

NOVEMBER**European Commission Honors Initiative on Tobacco Prevention**

The "Education against Tobacco (ACT)" initiative supported by the DZL receives the EU Health Award from the European Commission for its outstanding contribution to public health.

SEPTEMBER**DZL Board Member Tobias Welte Appointed as ERS President**

Prof. Dr. Tobias Welte assumes the presidency of the European Respiratory Society at the Annual Meeting in Paris.

OCTOBER**Millions of Euros to Support Excellent Lung Research**

Three DZL member institutions prevailed with medical applications in the multi-stage selection process of the German Excellence Strategy.



2018

DECEMBER**Inhalation Therapy Helps Infants with Cystic Fibrosis**

For the first time, a multicenter study carried out by the DZL demonstrates the benefit of preventive therapy, administered during early infancy before the onset of symptoms.

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.

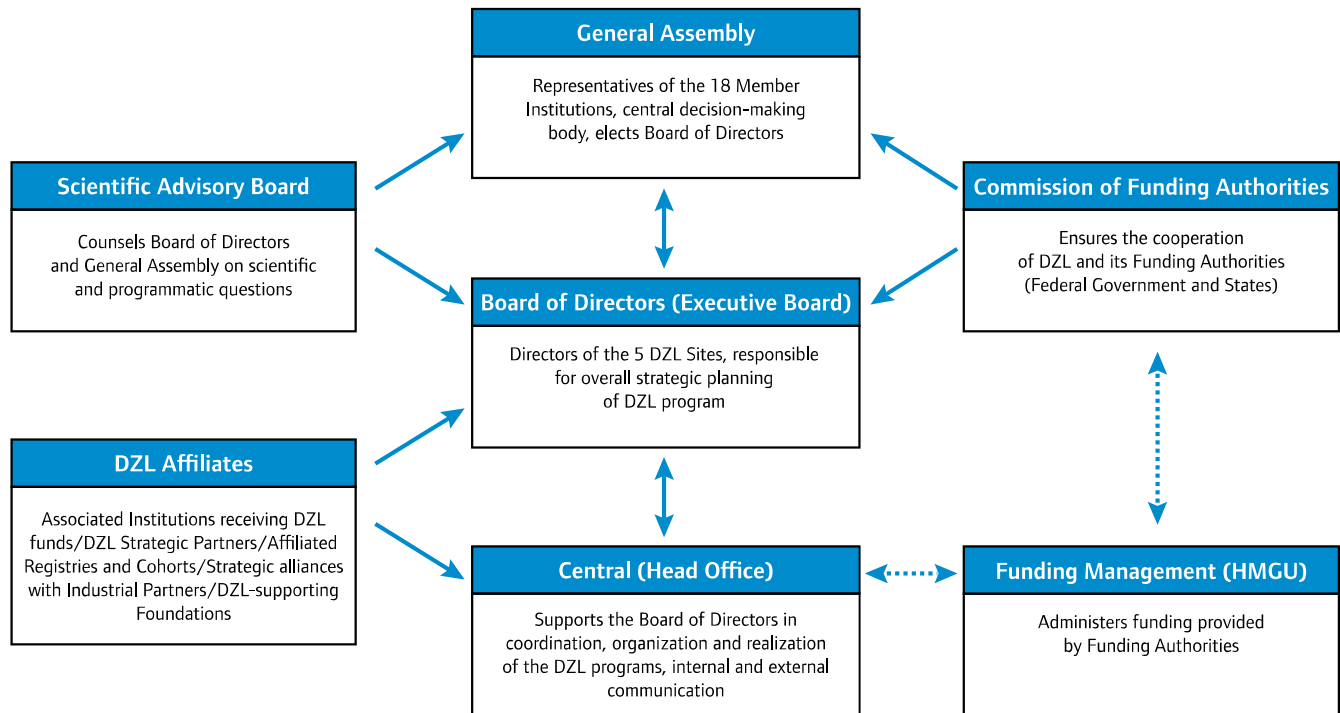
In 2009, the German Center for Neurodegenerative Diseases (DZNE) and the German Center for Diabetes Research (DZD) were founded. In 2011, four additional German Centers for Health Research were established: the German Center for Infection Research (DZIF), the German Center for Cardiovascular Research (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 at the German Academic International Network Conference 2018

DZL Organization



ARCN	BREATH	CPC-M	TLRC	UGMLC	6 further associated partners, nationally organized or based outside the DZL sites
4 Member Institutions + 3 Associated Partners	3 Member Institutions + 1 Associated Partner	3 Member Institutions + 1 Associated Partner	5 Member Institutions	3 Member Institutions	

DZL Executive Board

- Prof. Dr. Werner Seeger (DZL Chairman and Speaker) – Director of the DZL Site Giessen, Marburg, Bad Nauheim (Universities of Giessen and Marburg Lung Center, UGMLC)
- Prof. Dr. Hans-Ulrich Kauczor – Director of the DZL Site Heidelberg (Translational Lung Research Center, TLRC)
- Prof. Dr. Klaus F. Rabe – Director of the DZL Site Borstel, Grosshansdorf, Kiel, Lübeck, (Airway Research Center North, ARCN)
- Prof. Dr. Erika von Mutius – Director of the DZL Site Munich (Comprehensive Pneumology Center-Munich, CPC-M)
- Prof. Dr. Tobias Welte – Director of the DZL Site Hanover (Biomedical Research in Endstage and Obstructive Lung Disease, BREATH)

DZL Head Office

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

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 Jour-
nal 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, Biom-
etry 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 Criti-
cal Care Medicine Section, and courtesy professor of the
Department of Pathology and Microbiology and the Depart-
ment 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. Florian Mertes – Finance Department (Commercial
Funding Management, Helmholtz Zentrum München)

General Assembly

Currently, 18 member institutions belong to the DZL. In
addition, the DZL has eleven Associated Partners (as at
August 2019)

Commission of Funding Authorities

- German Federal Ministry of Education and Research: Chair
- Baden-Württemberg – Ministry of Science, Research and
the Arts Baden-Württemberg
- Bavaria – Bavarian State Ministry of 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 Education, Science and
Cultural Affairs

Selected Prizes and Awards

Award Winner	Award
Dr. Petros Christopoulos Heidelberg	Takeda Oncology Research Award for the best scientific work on non-small cell Lung Cancer (shared award)
Aufklärung gegen Tabak e. V.	EU Health Price awarded within the framework of the "EU Health Policy Platform"
Dr. Elie El Agha Giessen	"Von Behring Radiology Junior Award" for research projects in the area of Lung Fibrosis
PD Dr. Daniel P. Potaczek Marburg	Promtional Award of the DGAKI* "New Immunological Therapies on atopic and allergic diseases"
Prof. Dr. Tobias Welte Hannover	Assumed ERS** Presidency
Dr. Sabine Bartel Borstel	Marie-Curie-Fellowship for a two-years research project on epigenetic editing in the Netherlands
Prof. Dr. Matthias V. Kopp Lübeck	Assumed GPP*** presidency
Dr. Katrin Milger-Kneidinger München	DGP**** Research Award for the best clinical-therapeutical work (shared award)
Dr. Natascha Sommer Giessen	DGP**** Research Award in the field of fundamental research – best scientific work (shared award)
Dr. Herbert M. Schiller München	DGP**** Research Award in the field of fundamental research – best scientific work (shared award)
Dr. Rainer Glöckl München	DGP**** Poster Price, 2nd Price (shared award)
Prof. Peter Alter Marburg	DGP**** Poster Price, 2nd Price (shared award)
Dr. Thomas J. Bahmer Grosshansdorf	Sarcoidosis Research Award 2018 of the Sarcoidosis-Network e. V.
Dr. Rebecca Jurisch Giessen	Doctorate Price of the German Lung Foundation for the best experimental work
Dr. Inke König Lübeck	Dorothea Erxleben Research Award for innovative research projects

Abbreviations:

* Deutsche Gesellschaft für Allergie und Klinische Immunologie (German Society for Asthma and clinic Immunology)

** ERS - European Respiratory Society

*** Gesellschaft für Pädiatrische Pneumologie (Society for Pediatric Pneumology)

**** Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin (German Society for Pulmology and Respiratory Medicine)

DZL Member Institutions and Sites



Associated Partners of the DZL

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

DZL Site Borstel, Lübeck, Kiel, Grosshansdorf

Airway Research Center North (ARCN)

Partner Institutions of the Site

- Forschungszentrum Borstel - Leibniz Lung Center
- 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

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Research Profile

Scientists and clinicians of the Airway Research Center North (ARCN) focus on research on Chronic Obstructive Pulmonary Disease (COPD) and Lung Cancer as well as Asthma and Allergy. This translational research consortium combines top-level expertise in basic research and medicine in the field of pulmonology in Schleswig-Holstein. As the biggest North German clinic specializing in lung and airway diseases with more than 13,000 patients treated per year, the LungenClinic Grosshansdorf is, together with the University Clinic Schleswig-Holstein (UKSH) and the Medical Clinic Borstel, responsible for clinical and patient-oriented research in the ARCN. The Research Center Borstel focuses on the investigation of infectious as well as non-infectious lung diseases and contributes to the success of ARCN basic research and the development of animal models. Additional partners are researchers at the University of Lübeck and the Christian-Albrechts-University Kiel. These scientists test asthma in animal models, analyze the epigenetic 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 Lung-Clinic Grosshansdorf. To strengthen the connection between clinical and basic research, the Biomaterialbank Nord has been set up as a joint central infrastructure. In the field of asthma, our physicians for pediatric and adult lung medicine work closely together for a better understanding of different disease courses. This crosslink between complementary partners in the ARCN is intended to support the collaborative implementation of translational research strategies.

DZL Site Hanover

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), Hanover
- Leibniz University Hanover (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 Hanover (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)

Contact

DZL Site Coordinator, BREATH:

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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 Hanover 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:
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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
- Heidelberg University
- Thoraxklinik at Heidelberg University Hospital
- German Cancer Research Center (DKFZ)
- European Molecular Biology Laboratory (EMBL)

Prof. Dr. Hans-Ulrich Kauczor



- Director of the DZL site TLRC
- Provisional Director of the Department of Translational Pulmonology at Heidelberg University Hospital
- Medical Director of the Department of Diagnostic and Interventional Radiology at Heidelberg University Hospital Heidelberg

Contact

DZL Site Coordinator, TLRC:

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Research Profile

The Heidelberg Translational Lung Research Center (TLRC) is an interdisciplinary center for translational lung research, where physicians and scientists at Heidelberg University Hospital and the Medical Faculty of Heidelberg University, the Thoraxklinik at Heidelberg University Hospital (one of Germany's oldest and largest hospitals specializing in lung disease), 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 is focussed on 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 in the fields of Pulmonary Fibrosis, Pneumonia and Acute Lung Injury, and Pulmonary Hypertension. The scientists' goal is to identify new therapeutic targets to improve diagnostics and develop further 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. Current research investigates the mechanisms leading to airway mucus obstruction and chronic inflammation in Cystic Fibrosis and other chronic obstructive pulmonary 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 Biobanking and Imaging platforms are crucial to the success of the translational lung research program. Early clinical trials are conducted to make new diagnostic and therapeutic strategies available to patients as early as possible.

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

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Research Profile

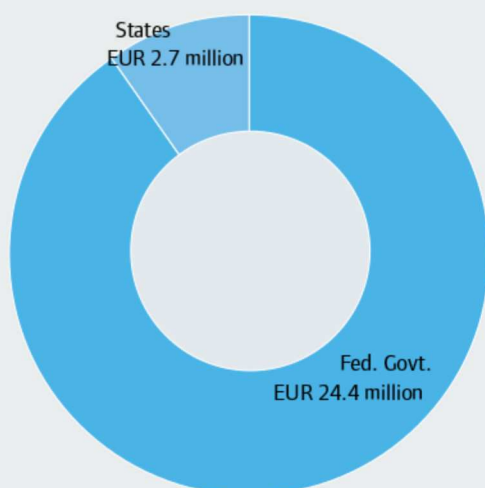
Translational research at the Universities of Giessen and Marburg Lung Center (UGMLC) focuses on lung diseases caused by inflammatory and hyperproliferative processes. This includes research on the antenatal and postnatal impact of environmental factors on the development of Asthma as well as on the development and therapy of Chronic Obstructive Pulmonary Disease (COPD), with 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 ALI, DPLD and PH. In the area PH, Giessen can be regarded as a center of national and international repute. 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

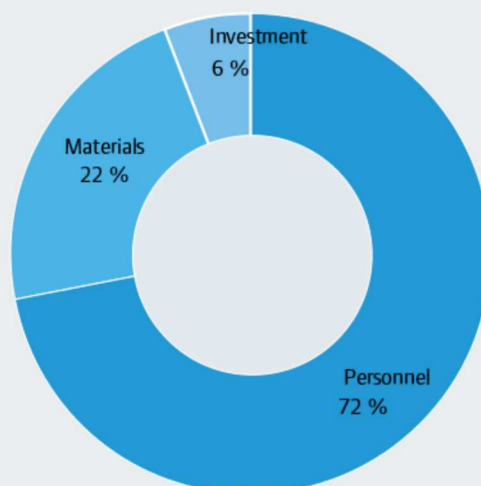
Total Funding and Cost Breakdown 2018

The total funding for the DZL in 2018 was 27.1 million euros. 90% was received from the German Ministry of Education and Research (BMBF) and 10% from the German states with participating DZL centers. Across the eight Disease Areas studied by DZL scientists, around 50 major research projects were supported. Finance is managed by the DZL Funding Management based at the Helmholtz Center in Munich. The Funding Management forwards the project funds to the DZL partner institutions. (As of June 2019)

Total Funding 2018



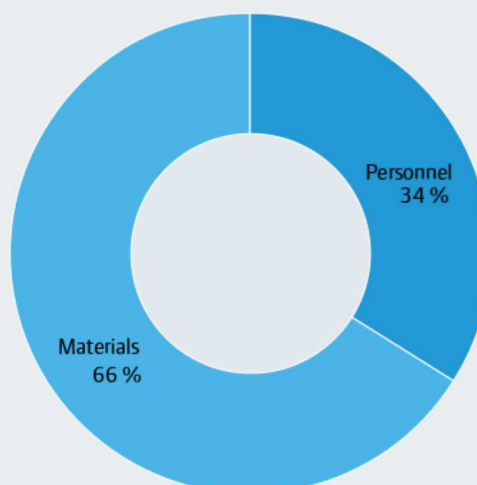
Cost Breakdown: DZL Expenses 2018



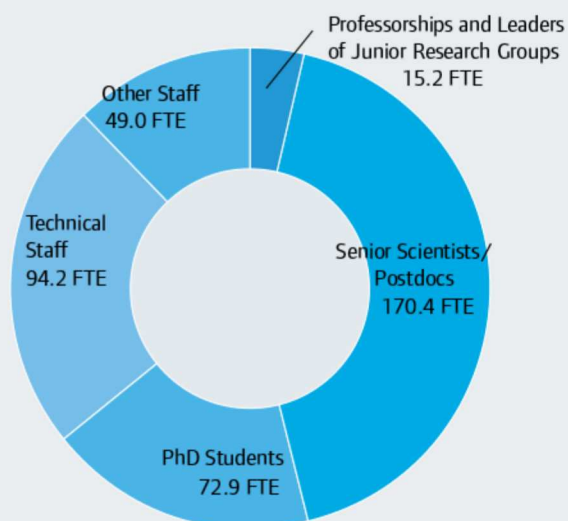
Cost Breakdown: DZL Expenses 2018

The DZL e. V. is financed through membership fees collected from each member institution as well as from donations. Membership fees amounted to €500,000 in 2018. The 2018 Annual Financial Statement and Year-End Close of the DZL was prepared by the firm Haas & Haas (Giessen)

Cost Breakdown: DZL e. V. Expenses 2018

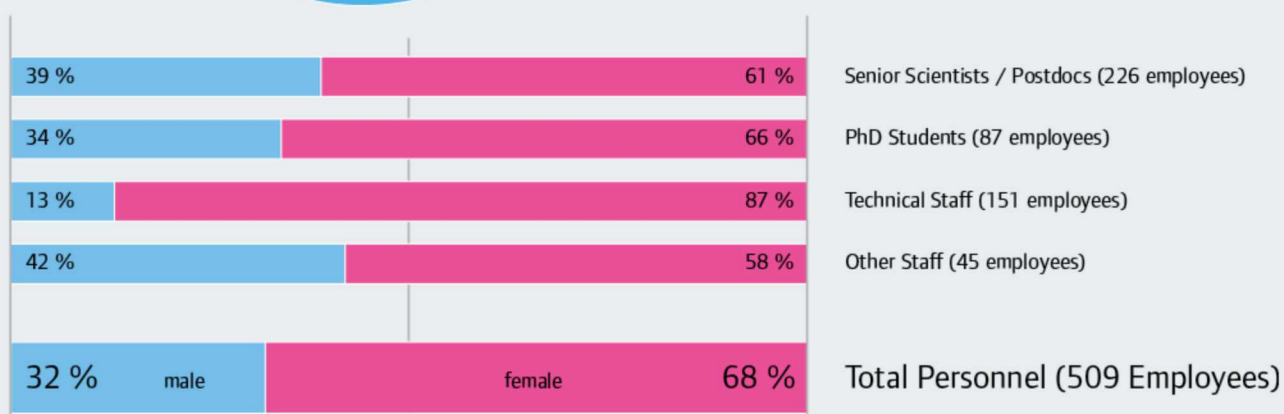


Personnel and Gender Equality 2018

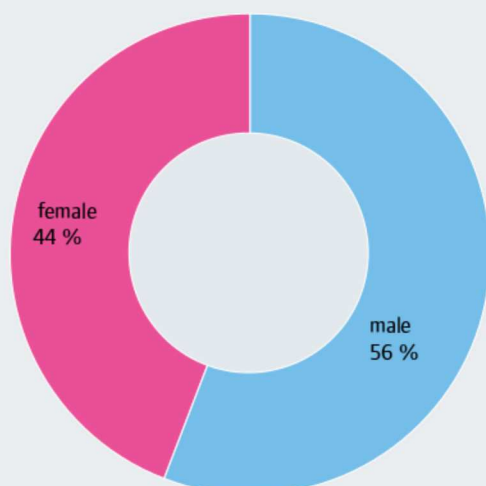


Personnel and Gender Equality 2018

In 2018, 525 employees (401.5 Full-Time Equivalents, FTE) were directly financed with DZL funds across the five partner centers. Of the 525 funded employees, 359 were women (68 % of total personnel).



Professorships and Leaders of Junior Research Groups 2018



Professorships and Leaders of Junior Research Groups DZL 2018

In 2018, there were 16 professorships and leaders of junior research groups funded within the DZL, 7 of whom were women (44 %).

Masthead

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Editorial Comment

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

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