

German Center for Lung Research

ANNUAL REPORT



2019

Translational Research to Combat Widespread Lung Diseases

Table of Contents

Foreword	2
Translation in the Focus of Research	3
Disease Areas	4
Asthma and Allergy.....	4
Chronic Obstructive Pulmonary Disease (COPD).....	6
Cystic Fibrosis (Mucoviscidosis).....	8
Pneumonia and Acute Lung Injury.....	10
Diffuse Parenchymal Lung Disease (DPLD).....	12
Pulmonary Hypertension.....	14
End-Stage Lung Disease.....	16
Lung Cancer.....	18
Platforms and Infrastructure	20
Biobanking & Data Management Platform.....	20
Imaging Platform.....	22
DZL Technology Transfer Consortium.....	25
Clinical Trial Board and Clinical Studies in the DZL.....	26
DZL Collaborations, Partnerships, and Networks	28
DZL Academy: Enabling Early Career Scientists	34
Equal Opportunities and Diversity	37
The Public Face of the DZL	38
DZL Highlights in 2019	42
The German Centers for Health Research	44
DZL Organization	45
Selected Prizes and Awards	47
DZL Member Institutions and Sites	48
Finance and Personnel	54

Foreword



*Prof. Dr. Werner Seeger
Chairman of the Board*



*Prof. Dr. Hans-Ulrich
Kauczor
Board Member*



*Prof. Dr. Klaus F. Rabe
Board Member*



*Prof. Dr. Erika v. Mutius
Board Member*



*Prof. Dr. Tobias Welte
Board Member*

Today, it no longer seems to be possible to look back on 2019 without the defining global experience with SARS-CoV-2. Everyone was confronted with questions both on a professional and a private level that had not yet been formulated in the wider society at the end of 2019: What holds us together as a society when daily personal contact must be avoided? Which parts of our society are systemically important? Which paths followed during the crisis will also allow us to make productive developments in the future?

COVID-19 bears the number of the past year in its name, even though the impact of this fatal infectious disease, primarily of the lungs and airways, was unforeseeable for Germany and the world last year. Since spring 2020 DZL physicians have been researching the decryption of SARS-CoV-2 and its consequences. In this report, however, we would first like to take a look at the numerous successes of the past year. In a joint study with the German Center for Cardiovascular Research (DZHK), a marker could be identified that predicts the mortality of COPD patients. In the area of Cystic Fibrosis, DZL researchers have developed an effective preventive therapy for infants. Such achievements in sight encourage each employee in each research area of the DZL in the long term to develop novel and life-saving approaches to the prevention, diagnosis, and treatment of patients with lung and airway diseases.

The DZL received special recognition in the past year by being honored with the internationally renowned Balzan Prize for the specialist field of "Pathophysiology of respiration: from basic sciences to the bedside". Besides the achievements in terms of new treatments and improvements in the quality of life of patients with lung disease, the enthusiasm of the young DZL generation of researchers was honored. We are very thankful for this honor. To pass part of this recognition directly on to the next DZL generation, we decided to support an intergenerational research project on the effects of e-cigarette use through the prize money and further DZL funding.

We would like to invite you to explore this as well as many other exciting research projects of the DZL, groundbreaking findings, and achievements in the combined efforts to combat widespread lung diseases in this Annual Report.

Giessen/Heidelberg/Grosshansdorf/Munich/Hanover in July 2020

The Board of the German Center for Lung Research

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 funded by the German Ministry of Education and Research (Bundesministerium für Bildung und Forschung, BMBF) and the federal states in which the corresponding 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 available therapies provide symptomatic relief but no cure for most airway diseases. This makes it all the more important to develop new approaches and options for disease prevention, diagnosis, and therapy by researching into the causes and mechanisms underlying these diseases. Research must address these challenges in a scientific and structurally coordinated manner to bring together expertise and treat lung diseases more successfully in the future. At the DZL, more than 240 principal investigators and their research groups currently work together to combat lung disease. Twenty-nine leading German research institutions at five different sites cooperate in this work.

Translational research at the DZL aims to better understand the causes of lung diseases and transfer findings from laboratory research into clinical practice more rapidly (bench to bedside). The focus is on eight Disease Areas. At the DZL, excellent university and non-university institutions cooperate closely for the benefit of the patient to rapidly develop new approaches to the treatment of lung disease. Basic researchers, whose primary goal is the gain of scientific knowledge, and clinical researchers, whose objective is the safe, successful application of new medical findings, collaborate more intensively than ever before. The DZL member and partner institutions work together on equal terms in joint research projects. Interdisciplinary teams look at lung diseases from various perspectives and close the gaps in the translational research chain. This close cooperation allows the researchers to conduct large-scale clinical studies with high numbers of subjects and access to large amounts of biomaterial and data for medical evaluation. In 2017, the German Council of Science and Humanities (Wissenschaftsrat) recognized that networked translational research provides major benefits, stating that the DZL should be further promoted without restrictions.





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 2019

- ✓ 15 joint publications of several DZL sites: partially achieved (11)
- ✓ 450 additional visits in the ALLIANCE asthma cohort
- ✓ 15 ongoing projects on the use of biomaterial and accompanying data
- ✓ Development of a DZL infrastructure for experimental microbiome research

Goals for 2020

- 10 joint publications of several DZL sites
- 450 additional visits in the ALLIANCE asthma cohort
- 15 ongoing projects on the use of biomaterial and accompanying data
- Microbiome description in animal models

Scientific Coordinators of the Disease Area

Prof. Dr. Susanne Krauss-Etschmann (ARCN)

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

Administrative Coordinator of the Disease Area

Dr. Jörn Bullwinkel (ARCN)

Participating DZL Partner Sites

all

Research Highlight 2019

Anti-inflammatory Effects of the Farm Environment

The prevalence of childhood asthma is significantly greater in urban areas compared with rural/farm environments. Murine studies have shown that TNF- α -induced protein 3 (TNFAIP3; A20), an anti-inflammatory regulator of nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) signaling, mediates environmentally induced asthma protection.

We aimed to determine the role of TNFAIP3 for asthma development in childhood and the immunomodulatory effects of environmental factors.

In a representative selection of 250 of 2,168 children from 2 prospective birth cohorts and 2 cross-sectional studies, we analyzed blood cells of healthy and asthmatic children from urban and rural/farm environments from Europe and China. PBMCs were stimulated *ex vivo* with dust from “asthma-protective” farms or LPS. NF- κ B signaling-related gene and protein expression was assessed in PBMCs and multiplex gene expression assays (NanoString Technologies) in isolated dendritic cells of schoolchildren and in cord blood mononuclear cells of newborns.

Anti-inflammatory TNFAIP3 gene and protein expression was consistently decreased, whereas proinflammatory toll-like receptor 4 expression was increased in urban asthmatic patients reflecting their increased inflammatory status. *Ex vivo* farm dust or LPS stimulation restored TNFAIP3 expression to healthy levels in asthmatic patients and shifted NF- κ B signaling-associated gene expression toward an anti-inflammatory state. Farm/rural children had lower expression, indicating tolerance induction by continuous environmental exposure. Children with asthma at school age had reduced TNFAIP3 expression at birth, suggesting TNFAIP3 as a possible biomarker predicting subsequent asthma.

Our data indicate TNFAIP3 as a key regulator during childhood asthma development and its environmentally mediated protection. As environmental dust exposure conferred the anti-inflammatory effects, it might represent a promising future agent for asthma prevention and treatment.



Children who grow up on the farm or in rural areas are often protected from allergies and asthma.

Further Information:

✉ Krusche J, Twardziok M, Rehbach K, Böck A, Tsang MS, Schröder PC, Kumbrink J, Kirchner T, Xing Y, Riedler J, Dalphin J-C, Pekkanen J, Lauener R, Roponen M, Li J, Wong CK, Wong GWK, Schaub B, Ege M, Depner M, Illi S, Loss GJ, Renz H, Pfefferle PI, Kabesch M, Genuneit J, Karvonen AM, Hyvärinen A, Kirjavainen PV, Remes S, Braun-Fahrlander C, Roduit C, Frei R, Kaulek V, Dalphin M-L, Divaret-Chauveau A, Doekes G (2019) TNF- α -induced protein 3 is a key player in childhood asthma development and environment-mediated protection. *J Allergy Clin Immunol* 144: 1684-1696.e1612



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.

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.

Goals achieved in 2019

- ✓ Completion of the iNOS-EMAPII study (success expected in 2020)
- ✓ 20 joint publications of several DZL sites: exceeded (24)
- ✓ 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

Goals for 2020

- 20 joint publications of several DZL sites
- Conference calls every two months for research coordination
- Joint project with the population-based Hamburg City Health Study to study risk factors (such as COPD) in COVID-19 patients
- Identification of comorbidity clusters in COSYCONET using AI
- Long-term study of COSYCONET patients regarding the dimension of lung change and identification of progression parameters

Scientific Coordinators of the Disease Area

Prof. Dr. Klaus F. Rabe (ARCN)

Prof. Dr. Claus F. Vogelmeier (UGMLC)

Administrative Coordinator of the Disease Area

Dr. Jörn Bullwinkel (ARCN)

Participating DZL Partner Sites

all

Research Highlight 2019

Troponin I Predicts All-Cause Mortality of COPD Patients – Collaborative Study of DZL and DZHK Published

Pneumologists of the German Center for Lung Research (DZL) and cardiologists of the German Center for Cardiovascular Research (DZHK) conducted a study on serum troponin I as a predictor of mortality in COPD patients, evaluating a wide range of cardiovascular and respiratory markers. The study within the framework of COSYCONET was published recently in the *European Respiratory Journal*.

Troponins are released as a result of heart injury or necrosis. This makes extremely high troponin levels a marker for the diagnosis of acute myocardial infarction. Many COPD patients also suffer from cardiovascular comorbidities. Therefore, scientists from the DZL and the DZHK hypothesized that serum level of high-sensitivity Troponin I (hsTI) might also have informative power in COPD patients. Actually, they found that stable COPD patients with higher hsTI concentration had higher all-cause mortality compared to patients with lower concentration. Intriguingly, this correlation was independent from concomitant heart disease. The significance became even higher when further parameters were taken into account. In the future, this result might help detect high-risk patients earlier.

Although the mechanistic background remains unclear, it is known that troponin is released from the heart. Therefore, COPD patients with higher hsTI levels should get regular check-ups of basic parameters like blood lipids ECG or long-term blood pressure to identify possibly overlooked cardiovascular disease. These patients should also see their pneumologist regularly to reduce the exacerbation risk and improve symptom control.

For this project, researchers analysed data and biosamples of more than 2,000 patients of the COSYCONET study, which is part of DZL. Regarding the collaboration of the DZL and DZHK, four of five DZL sites were involved. The paper published in the *European Respiratory Journal* is among the highest ranking publications of two or more German Health Centers.

Further Information:

Waschki B, Alter P, Zeller T, Magnussen C, Neumann JT, Twerenbold R, Sinning C, Herr C, Kahnert K, Fähndrich S, Blankenberg S, Rabe KF, Welte T, Jörres RA, Vogelmeier CF, Bals R, Watz H (2020) High-sensitivity troponin I and all-cause mortality in patients with stable COPD: an analysis of the COSYCONET study. *Eur Respir J* 55: 1901314



Analysis of serum samples



Cystic Fibrosis (Mucoviscidosis)

Goals achieved in 2019

- ✓ Elucidation of the dysbiosis (imbalance) of the CF airway microbiome submitted for publication
- ✓ 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 submitted for publication
- ✓ Impact of gene-gene interactions on the CF disease-modifying activity of the epithelial sodium channel ENaC submitted for publication
- ✓ Search for novel compounds that activate the alternative chloride channels SLC26A9 by high-throughput screening: first candidate compounds validated in CF airway epithelial cells
- ✓ Role of Interleukin-17 (IL-17) in the pathogenesis of CF lung disease submitted for publication
- ✓ New method for the assessment of free and membrane-bound neutrophil elastase as a biomarker of lung disease activity in CF published
- ✓ Recruitment for the first randomised controlled clinical trial (RCT) for evaluating the efficacy of the CF modulators Lumacaftor and Ivacaftor in preschool children with CF homozygous for the F508del mutation in cooperation with Vertex Pharmaceuticals (VX16-809-121) completed

Cystic Fibrosis (CF) is the most common genetically determined, early onset and still life-limiting form of chronic obstructive lung 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 over 40 years. The recent breakthrough in the development of therapies (CFTR-Modulators) that target the causal basic defect of cystic fibrosis will significantly improve the quality of life and lifespan of people with cystic fibrosis in the future. Despite the emergence of these new treatments, the disease is still incurable, and important questions with regard to the cause and progression of mucus obstruction, inflammation, and infection of the airways remain to be resolved. The overall aim of the DZL CF research program is to advance the current understanding of CF pathogenesis and use this knowledge to improve CF diagnostics, develop more sensitive tools for monitoring disease activity, and develop novel strategies for the effective prevention and therapy of CF.

Scientific Coordinators of the Disease Area

Prof. Dr. Marcus Mall (BIH)

Prof. Dr. Burkhard Tümmler (BREATH)

Administrative Coordinator of the Disease Area

Dr. Birgit Teucher (TLRC)

Participating DZL Partner Sites

ARCN, BREATH, TLRC, UGMLC

Research Highlight 2019

First Preventive Inhalation Therapy Helps Infants With Cystic Fibrosis

People with the incurable hereditary disease Cystic Fibrosis (CF) suffer from the progressive decline of their lung function and quality of life. The underlying genetic defect changes the composition of mucus inside the airways, making it more viscous. This thick mucus blocks the airways of patients and promotes bacterial growth, resulting in recurring infections that become chronic and eventually destroy the lungs. In order to delay and attenuate permanent lung damage, it is important to treat patients as early as possible.

Since 2016, newborns in Germany have been routinely screened for CF. Early diagnosis opens a new window for the application of preventive therapies for infants with CF. However, the development of such therapies has been hindered by the lack of non-invasive methods to assess the effects of therapeutic interventions. In 2017, researchers of Heidelberg University Hospital were able to show that non-invasive methods such as the determination of the lung clearance index (LCI) and magnetic resonance imaging are suitable to evaluate therapy effects in children. Their work paved the way for the first randomized controlled trial (RCT) on the preventive treatment of infants with CF. Scientists from four DZL sites (TLRC, ARCN, BREATH, UGMLC) showed that the inhalation of highly concentrated (hypertonic) saline was safe and influenced lung function as well as thriving of infants with CF positively. Additionally, LCI measurements proved to be a useful and sensitive outcome measure to monitor lung function in the context of RCTs in infants.

In total, 42 infants with CF participated in the study and were randomly assigned to either a control or therapy group. Twice

a day, the control group inhaled isotonic (0.9%) saline, while the therapy group inhaled hypertonic (6%) saline, with a salt concentration well above that of lung secretions. Inhalation of highly-concentrated saline promotes an influx of water into the airways, moisturises the mucus and mobilises it. This way, it supports the self-cleaning mechanisms of the bronchi. Over a period of 12 months, the lung function of infants in the therapy group followed the natural progression of healthy infants. However, the average lung function in the control group remained comparable to the baseline, which means that it worsened compared to the therapy group and healthy infants. At the end of the study year, infants who inhaled hypertonic saline were on average 1.5 cm taller and 500 g heavier than those of the control group, indicating an improvement of their overall well-being. Further studies will clarify whether preventive therapy can delay or even prevent irreversible lung damage in CF patients.

The lead author of this study, Dr. Mirjam Stahl, who worked as pediatrician and specialist in respiratory diseases in children at Heidelberg University Hospital, was honored for her work with two research prizes in 2019. She received the research prize of the German Respiratory Society (DGP) for the best clinical work and the Klosterfrau Research Grant.

Further Information:

Stahl M, Wielpütz MO, Ricklefs I, Dopfer C, Barth S, Schlegtendal A, Graeber SY, Sommerburg O, Diekmann G, Hüsing J, Koerner-Rettberg C, Nährlich L, Dittrich AM, Kopp MV, Mall MA. (2019) Preventive Inhalation of Hypertonic Saline in Infants with Cystic Fibrosis (PRESIS). A Randomized, Double-Blind, Controlled Study. *Am J Respir Crit Care Med* 199(10):1238-1248.

Stahl, M., Wielpütz, MO., Graeber, SY, Joachim, C., Sommerburg, O., Kauczor, HU., Puderbach, M., Eichinger, M., Mall, MA. (2017) Comparison of Lung Clearance Index and Magnetic Resonance Imaging for Assessment of Lung Disease in Children with Cystic Fibrosis. *Am J Respir Crit Care Med* 195(3):349-359.

Goals for 2020

- Epigenetic immunoprofiling of T-cell receptor repertoire and methylome of monozygous CF twins
- Comparison of the respiratory tract microbial community structures in healthy and CF preschool children
- Comparison of organoid swelling and in vivo biomarkers of CFTR function to determine therapeutic effects of CFTR modulators
- Determine effects of lumacaftor/ivacaftor on changes in lung structure and function, and airway microbiome in F508del homozygous patients with CF
- Determine the role of the ubiquitin ligase NEDD4.2 in the pathogenesis of mucociliary dysfunction



Pneumonia and Acute Lung Injury

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 fail-

ure. 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.

Goals achieved in 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 in patients with severe viral pneumonia
- ✓ Completion of recruitment of the PROGRESS cohort (2,300 patients) and of the PROGNOSIS cohort (1,250 patients)
- ✓ Start of recruitment of the global CIGMA phase III trial on immunoglobulin treatment of patients with severe pneumonia

Scientific Coordinators of the Disease Area

Prof. Dr. Susanne Herold (UGMLC)

Prof. Dr. Tobias Welte (BREATH)

Administrative Coordinator of the Disease Area

Dr. Sylvia Weißmann (UGMLC)

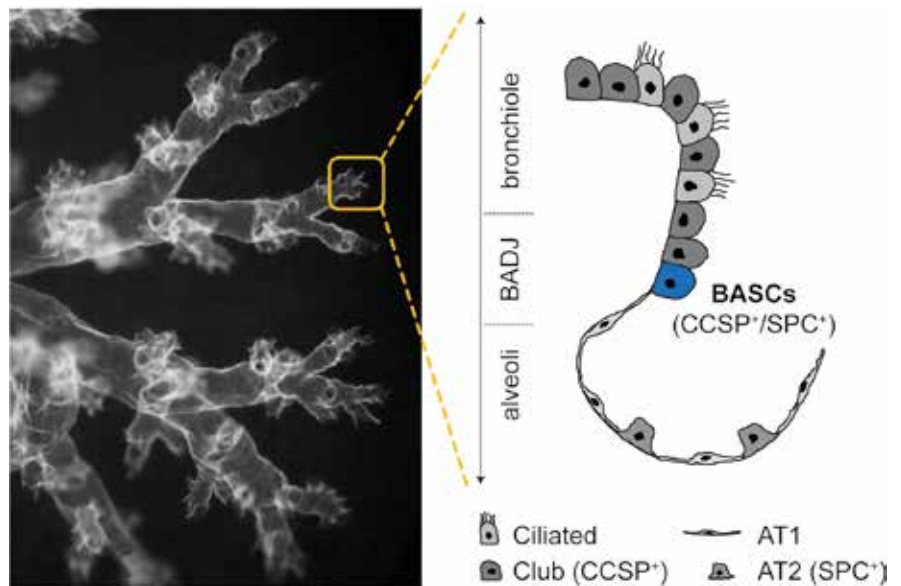
Participating DZL Partner Sites

all

Research Highlight 2019

Bronchoalveolar Stem Cells Are a Source For Regeneration of Lung Epithelia After Sterile and Infectious Lung Injury

Effective fostering of repair mechanisms in the injured and infected lungs requires the identification and functional characterization of endogenous stem cells recruited to drive lung regeneration processes. Bronchoalveolar stem cells (BASCs) have been considered a potential source for lung regeneration, however, direct *in vivo* evidence of multipotential lineage contribution during homeostasis and disease has been critically missing, since specific genetic labeling of BASCs has not been possible. We developed a novel cell tracing approach allowing for the selective targeting of dual-marker expressing BASCs in mouse lungs. RNA sequencing of isolated BASCs demonstrates that BASCs show a distinct transcriptional profile, characterized by co-expression of bronchiolar (Club cell) and alveolar epithelial (alveolar epithelial type 2 cell) genes. We found that BASCs generate the majority of distal lung airway cells after bronchiolar damage but only moderately contribute to cellular turnover under homeostatic conditions. Importantly, diphtheria-toxin a-chain (DTA)-mediated ablation of BASCs compromised proper regeneration of distal airways. Influenza virus-induced lung damage destroyed BASC cell populations as well, slowing down regeneration. Our RNA-seq analysis demonstrated that BASCs co-express many genes that were assumed to be characteristic of either AT2 or Club cells, indi-



cating that BASCs represent a progenitor cell type, which is locked in a plastic intermediate state, enabling it to differentiate into two different lineages.

The study defines BASCs as crucial components of the lung repair machinery both after sterile and infectious lung injury and provides a paradigmatic example of the detection and manipulation of stem cells that cannot be recognized by a single marker alone.

Goals for 2020

- Identification and molecular characterization of macrophage-associated repair factors (e.g. PLET1) for therapeutic use in patients with severe viral pneumonia
- Translation of basic scientific and preclinical knowledge for the antiviral effect of inhaled liposomal cyclosporine A (CsA) against SARS-CoV-2 in a pilot study on the treatment of patients with early symptomatic COVID-19 disease (L-CsA-I-COVID)
- Establishment of a clinical study (first patient in 2020) to prevent COVID-19 progression to ARDS through the inhalation of growth factor GM-CSF (GI-COVID)

Further Information:

Salwig I, Spitznagel B, Vazquez-Armendariz AI, Khalooghi K, Guenther S, Herold S, Szibor M, Braun T (2019) Bronchioalveolar stem cells are a main source for regeneration of distal lung epithelia *in vivo*. *EMBO J* e102099, DOI 10.15252/embj.2019102099



Diffuse Parenchymal Lung Disease (DPLD)

Diffuse Parenchymal Lung Disease (DPLD), or Interstitial Lung Disease (ILD), comprises a group of over 200 different lung diseases most often resulting in severe illness. DPLDs are mainly characterized by progressive scarring of the lung architecture and result from acute or chronic lung damage in children and adults. The lung damage may be caused by the influence of toxic gases or dusts or as a result of therapeutic measures (e.g. mechanical ventilation or radiation therapy). In many cases, however, the cause remains unclear, e.g. with Idiopathic Interstitial Pneumonias (IIPs), which also comprise Idiopathic Pulmonary Fibrosis (IPF).

Although the cause of DPLDs varies, the course is similar as the disease progresses and is associated with poor prognosis. First antifibrotic treatments for IPF slow down scarring in the lungs, which can be prognostically relevant; however, they are not able to stop this process. Currently, the only curative treatment is lung transplantation carried out at specialized centers. The DPLD Disease Area of the DZL involves the structured collaboration of internationally renowned theoretical researchers and clinicians across the sites for both pediatric and adult forms of DPLDs. On the one hand, this collaboration serves to better understand disease-relevant processes and the molecular reactions and cellular interactions behind them. On the other hand, algorithms for the early detection of disease-related and prognostically relevant changes as well as personalized treatment and follow-up concepts are developed. The DPLD

Disease Area has accepted the challenge to better understand and diagnose fibrotic lung diseases from birth through to old age while identifying special reparative and regenerative processes that may be used for future treatment concepts.

[Scientific Coordinators of the Disease Area](#)

Prof. Dr. Andreas Günther (UGMLC)

PD Dr. Anne Hilgendorff (CPC-M)

[Administrative Coordinators of the Disease Area](#)

Franziska Hauptkorn (CPC-M)

Dr. Jutta Schlegel (UGMLC)

[Participating DZL Partner Sites](#)

BREATH, CPC-M, TLRC, UGMLC

Research Highlight 2019

Genetic Markers of Fibrosis Development to Assess the Risk of the Course of the Disease

Idiopathic Pulmonary Fibrosis (IPF) is a fatal illness with a variable and unpredictable course. Prof. Dr. Prasse and his colleagues have now determined whether gene expression of specific cells from bronchoalveolar lavage (BAL) may predict survival in patients with IPF. The retrospective study analyzed the BAL transcriptome of three independent IPF cohorts: Freiburg (Germany), Siena (Italy), and Leuven (Belgium) with 212 patients. BAL cells from 20 healthy volunteers, 26 patients with sarcoidosis stages III and IV, and 29 patients with Chronic Obstructive Pulmonary Disease (COPD) were used as control subjects. Survival analysis showed that a total of 1,582 genes were predictive of mortality with great accuracy in the IPF patient cohort. A nine-gene signature was then characterized in one cohort (Freiburg) and confirmed in the other cohorts.

The genes associated with mortality of the patients in the BAL cells were indicative of a potential role of airway basal cells in this disease. Further analyses using gene expression, flow cytometry, and immunohistochemistry confirmed the disease-

specific increase in airway basal cells in BAL and lung tissue of IPF patients, which could not be shown in patients with COPD or sarcoidosis. The results identify and validate a characteristic BAL gene signature of patients with Idiopathic Pulmonary Fibrosis (IPF) that predicts mortality in IPF and improves the accuracy of outcome prediction based on clinical parameters. The BAL signature associated with mortality unmask a potential role of airway basal cells in IPF.

Further Information:

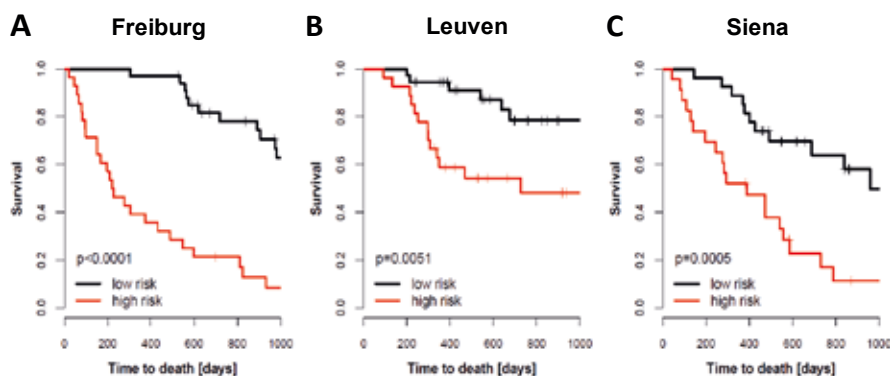
Prasse A et al (2019). BAL Cell Gene Expression Is Indicative of Outcome and Airway Basal Cell Involvement in Idiopathic Pulmonary Fibrosis. *Am J Respir Crit Care Med.* 2019 Mar 1;199(5):622–630. doi: 10.1164/rccm.201712-2551OC.

Goals achieved in 2019

- ✓ Development of new genetic and imaging markers for risk stratification in pediatric and adult DPLD cohorts
- ✓ Completion and publication of the clinical RELIEF study; successful continuation of the pilot study on the exacerbation of pulmonary fibrosis
- ✓ Establishment of new disease models (*in vivo* and *ex vivo*) incl. stem cell organoids
- ✓ Development of markers and cellular therapies of damage to the epithelium and fibroproliferation (interactome atlas)

Goals for 2020

- Characterization of alternative macrophage activation, inflammasome, and programmed cell removal in DPLD considering environmental effects
- Characterization of epithelial-mesenchymal crosstalk with a focus on epithelial-cellular plasticity in neonatal and adult DPLD
- Establishment of (pre)clinical studies to evaluate new diagnostic tools in fibrosis (single-cell analysis, biomarkers) taking into account comorbidities (PH), development of algorithms using AI
- Use of experimental disease models incl. stem cell organoids using second hits (virus, small particle exposure) with an important emphasis on macrophage activation



The 165 genes associated with the survival signature suggest a role for airway basal cells. On the basis of this selection a prediction model was developed in the Freiburg cohort (A), which was validated in the Leuven (B) and Siena cohort (C).



Pulmonary Hypertension

Pulmonary Hypertension (PH) is a disease of the pulmonary vasculature, leading to shortness of breath, dizziness, fainting, and right heart failure. Pathological thickening of the pulmonary vasculature increases pressure in the pulmonary circulation. Cell types of all vascular layers are affected; to be named are the overgrowth (pseudomalignant proliferation) of smooth muscle cells in the vessel wall as well as changes to the endothelial cells and fibroblasts. Moreover, there is a large number of inflammatory cells in the vessel wall contributing to its remodeling. All this leads to a severe loss of the cross-sectional area of the vessels and an increase in right ventricular after-

load. Currently available PH therapy relies on vasodilators that can be administered alone or in combination. Symptomatic relief does improve life expectancy; however, it is not possible to reverse the structural changes and restore functional integrity of the pulmonary vasculature. Understanding the cellular causes and restoring the vascular structure and function (reverse remodeling) is the main goal of the research work carried out by the PH team.

Goals achieved in 2019

- ✓ Description of the kinase profile of vessel cells and identification of new tyrosine and serine/threonine kinases, which serve as target structures for new therapeutic approaches
- ✓ Preclinical and clinical studies on the treatment of cigarette-smoke-induced pulmonary emphysema with the stimulator of soluble guanylate cyclase riociguat
- ✓ Clinical investigations for PH monitoring using a new form of sensors (Single Point Cardiodynamics, SPC)
- ✓ Clinical studies with vasodilators (prostacyclin analogs, endothelin receptor antagonists, stimulators of soluble guanylate cyclase) in different forms of Pulmonary Hypertension

Scientific Coordinators of the Disease Area

Prof. Dr. H. Ardeschir Ghofrani (UGMLC)

Prof. Dr. Ralph T. Schermuly (UGMLC)

Administrative Coordinator of the Disease Area

Dr. Sylvia Weißmann (UGMLC)

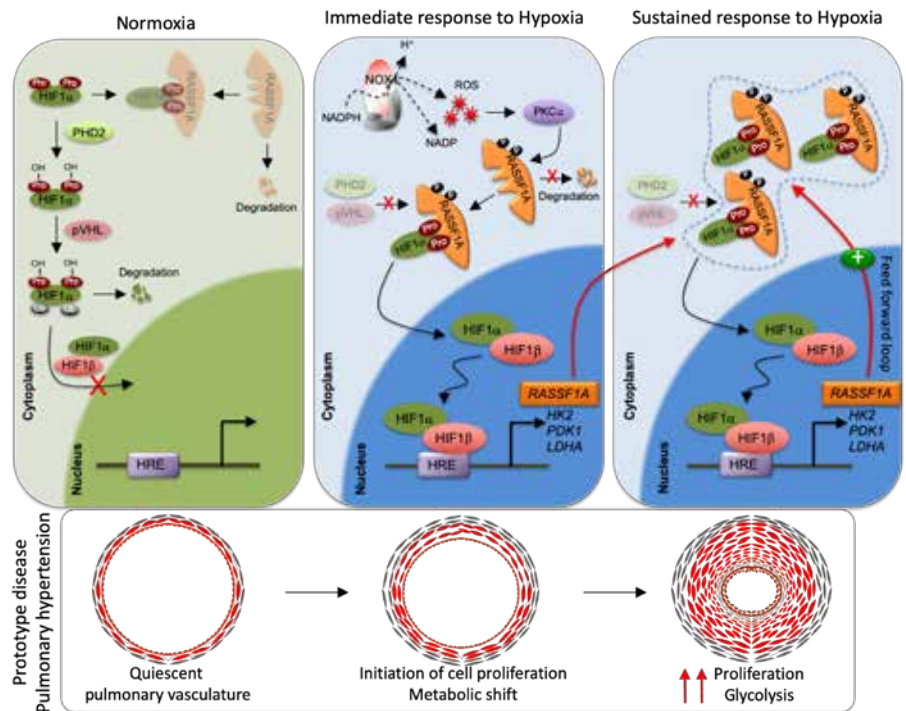
Participating DZL Partner Sites

all

Research Highlight 2019

A RASSF1A-HIF1 α Loop Drives Warburg Effect in Cancer and Pulmonary Hypertension

Hypoxia signaling plays a fundamental role in non-malignant and malignant hyperproliferative diseases like pulmonary hypertension, cancer, chronic lung disease, ischemic heart disease, stroke, and congestive heart failure. Physiologically, hypoxia stabilizes the hypoxia-inducible factor (HIF) facilitating oxygen delivery and adaptation to hypoxia by regulating a wide spectrum of cellular and tissue hypoxia responses. These include the stimulation of red blood cell production and angiogenesis as well as induction of glycolysis and reductions in fat and mitochondrial metabolism. Under disease conditions, hypoxia induces changes in gene expression in target organs that either fail to result in adequate adaptation or directly contribute to disease pathogenesis. The team of Dr. Pullamsetti is interested in HIF stability and signaling; it demonstrated that hypoxia promotes stabilization of Ras association domain family 1A (RASSF1A) through NOX1-dependent and protein kinase C-dependent phosphorylation. RASSF1A is a scaffold protein that acts as a tumor suppressor and binds to HIF-1 α , blocks its prolyl-hydroxylation and proteasomal degradation, and thus enhances the activation of the glycolytic switch (Warburg effect). They found that this mechanism operates in experimental hypoxia-induced PH, which is blocked in RASSF1A knockout mice, in human primary PH vascular cells, and in a subset of human lung cancer cells.



Collectively, this study identifies a hitherto unrecognized crucial role of RASSF1A in regulating HIF-1 α , and to promote hypoxia-driven gene regulation, metabolic switch and hyperproliferation in Pulmonary Hypertension as a non-malignant hypoxia-induced prototype disease and Lung Cancer. The underlying molecular mechanisms unveiled here (Figure 1) provide future targets for therapeutic intervention, which are to be exploited for improved therapy of these diseases.

Further Information:

✉ Dabral S, Muecke C, Valasarajan C, Schmoranzner M, Wietelmann A, Semenza GL, Meister M, Muley T, Seeger-Nukpezah T, Samakovlis C, Weissmann N, Grimminger F, Seeger W, Savai R, Pullamsetti SS. Nat Commun. 2019 May 13;10(1):2130. doi: 10.1038/s41467-019-10044-z.

Goals for 2020

- Preclinical experiments on the role of Janus kinases, which were identified in 2019 in PH
- Development of new therapies for Pulmonary Hypertension caused by cigarette smoke with a focus on NADPH oxidases
- Epigenetic studies of vascular cells in PH
- Clinical functional and imaging studies on the role of the right heart in different forms of PH



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. In general, ECMO therapy remains restricted to short-term application, primarily as a bridge to transplantation or as a bridge to recovery in acute pulmonary infections (e.g. caused by influenza or COVID-19). According to the latest findings, both procedures also offer the option of lung regeneration. In chronic lung injury, transplantation remains the only available therapy with the potential of true long-term survival. However, also as a result of the lack of donor organs, it is limited to certain patients and excluded

in lung tumors, for example. Long-term survival after lung transplantation is also highly threatened by chronic rejection. Current research aims to 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. The problem of the lack of donor organs is to be addressed with xenotransplantation in the future. Another area of research is the colonization of decellularized lungs with in vitro cultured cells of the recipient (called tissue engineering). Furthermore, stem cell therapy is hoped to enable lung tissue regeneration.

Goals achieved in 2019

- ✓ Consensus paper on restrictive allograft syndrome (RAS) and on pediatric PH
- ✓ Multicenter study: portable normothermic *ex-vivo* lung perfusion, ventilation, and functional assessment of donor lungs according to extended LTx criteria with the Organ Care System
- ✓ 3D histology of the pig lung for tissue pressure
- ✓ Establishment of a small animal model on veno-venous ECMO
- ✓ Establishment of ECMO therapy as a “bridge to recovery” of autologous lungs

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 2019

Use of a Perioperative Veno-Arterial ECMO Protocol in Patients with Acute Massive Bilateral Pulmonary Embolism

Acute bilateral pulmonary embolism is a rare disease, which may be life-threatening due to the concomitant cardiogenic shock with consecutive compromising of further organs (e.g. liver, kidneys). The surgical treatment of choice, called Trendelenburg operation, is associated with very high mortality, not least because of hemodynamic and respiratory instability of the patients, who are sometimes also subjected to lysis therapy before surgery. For this reason, initial sole systemic lysis therapy



Figure 2: Surgically removed thrombus material in acute pulmonary embolism

is the current gold standard, while this does not always result in the desired immediate hemodynamic stabilization and many patients will need reanimation. To optimize treatment of these patients, the “Pulmonary Embolism Response Team (PERT)”, an interdisciplinary team of cardiac surgeons, pulmonologists, cardiologists, and radiologists, was established in Hanover in 2012. Together they evaluate and decide about the therapeutic options of acute pulmonary embolism for each individual patient. In the same year, a treatment protocol focusing on veno-arterial extracorporeal membrane oxygenation (ECMO) for

Goals for 2020

- Ex-vivo lung perfusion for immunomodulation in allogeneic lung transplantation
- ECMO therapy in COVID-19
- Psychosocial assessment and its predictive validity in lung transplantation
- Histopathological analysis of COVID-19 patients to identify the pathogenesis
- Projects across the sites on lung xenotransplantation

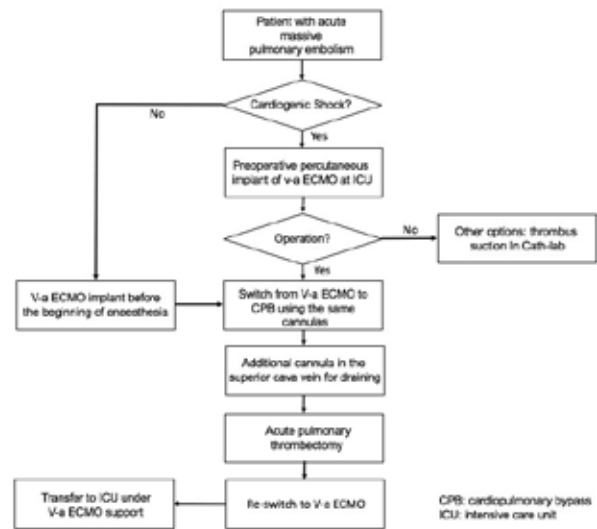


Figure 1: Flowchart of treatment in patients with acute pulmonary embolism

acute hemodynamic stabilization was developed in a patient with acute massive pulmonary embolism (Figure 1). Accordingly, patients with acute pulmonary embolism are stabilized with veno-arterial ECMO to also minimize the consequences of hemodynamic shock. After 1–3 days, surgical embolectomy is performed protected by veno-arterial ECMO support (Figure 2). The support is continued for another 2–3 days to slowly wean the patient from ECMO, i.e. adapt the patient’s circulation to the new situation. With ECMO support, patients can already be extubated in accordance with their hemodynamic and respiratory situation before ECMO is ended. Thirty-six patients with massive, life-threatening pulmonary embolism were included in the study between 2012 and 2018 and initially treated with veno-arterial ECMO. Nineteen (53%) of these patients had previously undergone unsuccessful systemic lysis therapy. In 20 (55%) of these patients, pulmonary embolectomy was performed. In line with the protocol, each of these patients was transferred to ICU with veno-arterial ECMO support. One (5%) patient died of sepsis, while all other patients were, on average, discharged from hospital after 22 days without any neurological abnormalities.

Further Information:

✉ Fabio Ius et al (2019) Extracorporeal membrane oxygenation and surgical embolectomy for high-risk pulmonary embolism. *Eur Respir J* 2019; 53: 1801773.



Lung Cancer

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 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. In biomarker-driven precision medicine, one major research goal is to identify non-invasively obtained biomarkers that predict response or potential failure to treatment in real time, such as the measurement of genetic tumor material in blood samples (liquid biopsy). Further research approaches are concerned with the elucidation of mechanisms that contribute to tumor evolution and therapy resistance. A better understanding of these mechanisms will form the basis of new drug developments and is essential for choosing the best possible combination therapy concept for each individual patient.

Goals achieved in 2019

- ✓ The treatment of decellularized extracellular matrix of fibroblast with TGF- β promotes the transition of epithelial to tumor cells (manuscript in progress).
- ✓ The antifibrotic drug pirfenidone inhibits the activation of the TGF- β signaling pathway and thus reduces tumor growth and tumor size (published).
- ✓ The characterization of the immunological microenvironment of ALK+ tumors continues into 2020.
- ✓ The enzyme mTOR promotes resistance to DNA-damaging drugs in lung cancer cells.
- ✓ A model that investigates environmental pollutants with lung cancer risk identified molecular alterations for the evolution of lung cancer on exposure to tobacco smoke and radiation.

Scientific Coordinators of the Disease Area

PD Dr. Rajkumar Savai (UGMLC)

Prof. Dr. Michael Thomas (TLRC)

Administrative Coordinator of the Disease Area

Dr. Birgit Teucher (TLRC)

Participating DZL Partner Sites

all

Research Highlight 2019

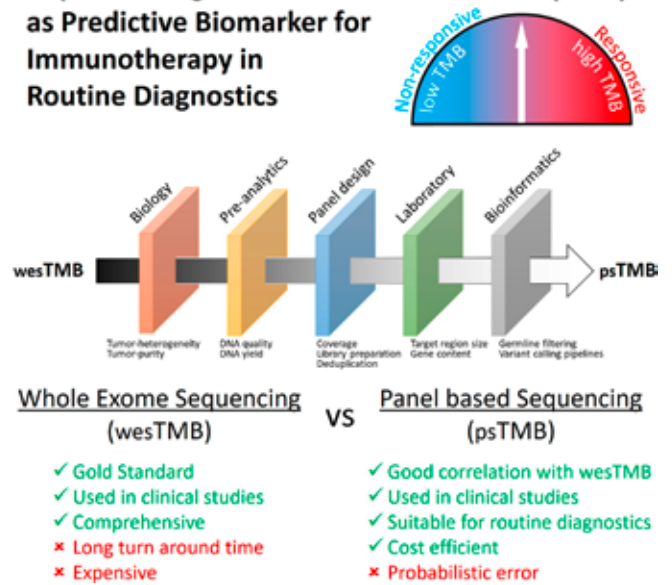
How Can a Patient's Response to Immunotherapy Be Predicted Better?

The aim of immunotherapy is to fight tumors with the help of the body's own immune system. Unfortunately, only about a quarter of the patients respond to currently available immunotherapies. It is an important goal to predict early on which patients will benefit from the treatment in the long-term, as it may have severe side effects.

Checkpoints of the immune system act as a brake and prevent overreaction of the immune system and concomitant damage of healthy tissue. Tumor cells take advantage of this mechanism and prevent an attack of the immune system by producing signal molecules that activate this brake. Antibodies against these signal molecules, so-called checkpoint-inhibitors, are applied in immunotherapy to override the tumor-initiated blockade and reactivate the body's own defense. The Prerequisite for the destruction of tumor cells by the immune system is that these are recognised as such. The more mutations a tumor cell accumulates, the more likely is the presentation of new structures, so-called neo-antigens, on the cell surface, which mark the tumor cell as a modified cell of the body. The total number of genetic changes (mutations) in a cancer cell compared to healthy tissue (called tumor mutational burden, TMB) could therefore be an important predictor for a patient's response to immunotherapy. The gold standard for the determination of TMB is to count all present mutations in a tumor cell by whole exome sequencing.

Since this procedure is very time-consuming and expensive, it is currently not possible to apply it in routine care. Therefore, scientists from the DZL site Heidelberg explored alternative

Implementing Tumor Mutational Burden (TMB) as Predictive Biomarker for Immunotherapy in Routine Diagnostics



Characteristics and influencing factors of TMB analysis

methods to estimate the TMB based on a selection of cancer-relevant genes. The scientists compared the TMB estimates determined by the new methods with TMB values of the gold standard in large patient groups. This way, they were able to specify mathematical regularities that describe how large the number of investigated genes has to be to obtain a reliable estimate of the TMB. As tumors are constantly evolving and also able to metastasize, the TMB was also analysed in multiple areas of a tumor. This analysis revealed that TMB varied in different areas of the same tumor. Indicating that TMB analysis based on single sample testing can be biased. Therefore, additional approaches for the analysis of blood are currently evaluated intensively.

Taken together, the complexity of the TMB biomarker requires very high-quality standards in lab diagnostics and bioinformatics analysis to obtain reliable estimate of the TMB.

Goals for 2020

- Characterization of the immunological microenvironment of wild-type and oncogene-driven tumors
- Investigation of tumor-associated macrophages in wild-type and oncogene-driven tumors
- Effect of tumor-infiltrating lymphocyte subpopulations on tumor progression
- Molecular characterization of lymphocyte subpopulations in biopsies obtained from patients undergoing immunotherapy
- Exploration of biomarker combination for the prognosis of response to tumor therapy based on the DZL-funded clinical trial "Early response capturing in the treatment of adenocarcinoma of the lung"

Further Information:

- ✉ Budczies J et al (2019) Optimizing panel-based tumor mutational burden (TMB) measurement. *Ann Oncol.* 30(9):1496-1506
- ✉ Kazdal D et al (2019) Spatial and Temporal Heterogeneity of Panel-Based Tumor Mutational Burden in Pulmonary Adenocarcinoma: Separating Biology From Technical Artifacts. *J Thorac Oncol.* 14(11):1935-1947



Biobanking & Data Management Platform

Goals achieved in 2019

- ✓ Full operation of the centralized DZL Data Warehouse, integration of additional databases with periodic updates
- ✓ Improvement of the data quality, ongoing harmonization of data (annotation, terminology, ontology)
- ✓ Further development of the harmonized catalog of clinical parameters, phenotypes and specimen, the Collaborative Metadata Repository (CoMetaR)
- ✓ Implementation of the DZL-integrative omics platform (DIOP)
- ✓ Networking activities with DZG biobanks
- ✓ Development of a Broad Informed Consent form for pediatric biobanking

Goals for 2020

- Prospective sampling of biospecimen and associated clinical data
- Integration of additional databases, cohorts, registries into the DZL Data Warehouse. Improvement of data depth and data quality.
- Implementation of disease-specific clinical core datasets
- Use of the DZL Data Warehouse as a service infrastructure (project planning, providing biomaterial and data)
- Training in biobanking issues
- Consulting in ELSI (medical ethics, data protection)

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

PD Dr. Karoline I. Gaede (ARCN)
Prof. Dr. Andreas Günther (UGMLC)

Administrative Coordinator

Dr. Jutta Schlegel (UGMLC)

Central Biobanking Management

Dr. Clemens Ruppert (UGMLC)

Central Data Management

Raphael Majeed (UGMLC)

Research Highlight 2019

Integration of an App-Based Electronic Questionnaire in a Clinical Setting

The need and use of patient-reported outcomes (PRO) has evolved rapidly in the past couple of years. Questionnaires are often used to assess quality of life, behavioral or sociodemographic items. Paper-based questionnaires are commonly used in clinical research, because they are easy to create and implement in a clinical setting. However, they lack in data quality, integrity and are time-consuming in making the data available. Data have to be transferred into research databases manually by medical staff, making questionnaire-based research cost-intensive, inefficient and sensitive to errors. Electronic devices, e.g. tablet PCs, can be a solution, since they can integrate plausibility controls, alter the questionnaire according to previously entered items, and check for completeness of data. Data transfer is efficient, since data are already available in an electronic format, and the electronic devices can be integrated into the existing clinical IT infrastructure.

However, integration of electronic devices into a clinical infrastructure is often cumbersome. Hurdles such as no or slow WiFi connectivity as well as IT-security issues need to be considered.

Within the DZL site BREATH, we developed the ASSIST-App – an app-based respiratory questionnaire installed on tablet PCs to address the shortfalls of time-consuming and error-prone paper-based surveys. At the same time, we also came up with an efficient solution for the integration into our clinical setting. Instead of linking the electronic devices directly to the local IT infrastructure, the app runs independently on tablet PCs: After completion of the questionnaire, a QR code is created, which contains the complete entered data. At any chosen time, using 2D barcode scanners, the data are transferred fast and without errors into a research database, where they can be processed for clinical use and research purposes. Data on the tablet PC are deleted completely after data transfer, so there is no need to care about IT-security or data protection issues. Using the ASSIST-App, we can efficiently assess demographic data, health-related quality of life (HRQoL), respiratory symptoms, pain, exposure to pollutants, smoking history, vaccination status, alcohol abuse, educational status, occupation, hospitalizations, exacerbations, health-specific tools like ACT (Asthma Control Test), CAT (COPD Assessment Test), NCCN Distress Thermometer or emPHasis10 as well as psychiatric disorders (HADS-A and HADS-D).

The ASSIST-App was piloted on May 10, 2019 in the asthma outpatient clinic and consecutively enrolled in all Disease Areas. Within one year, we conducted over 4,700 questionnaires,

of which ~1100 are baseline questionnaires. The median time of questionnaire completion duration was 09:53 min (IQR 6:40 – 15:03), and the median age of patients was 63 years (IQR 55-72). The ASSIST-App is therefore deemed to be a feasible and useful tool to create high-quality scientifically useable data in an efficient manner. And when used DZL-wide, large epidemiological studies are possible using the DZL Data Warehouse.



Tablet PC using the ASSIST-App after the questionnaire is completed. The QR Code is created and the patient is prompted to bring the tablet PC back to the clinical staff and disinfect hands afterwards.



Imaging Platform

DZL scientists have access to a wide range of innovative imaging technologies in microscopy and radiology to advance our knowledge of the emergence and development of lung diseases, to evaluate the efficacy of drugs, and to support drug-discovery processes. The Imaging Platform ensures the availability

Goals achieved in 2019

- ✓ Continuation of the imaging technologies portfolio for prospective clinical studies (ongoing)
- ✓ New imaging biomarkers for the diagnosis and monitoring changes of the airways published (ongoing)
- ✓ Human Lung Atlas – working program established
- ✓ DZL Platform Imaging Workshop knowledge transfer of state-of-the-art imaging technologies and methodologies
- ✓ Facilitating closer links and transition from preclinical, translational and clinical imaging (ongoing)

Goals for 2020

- Facilitating interdisciplinary exchange by organizing a meet-the-imaging expert session at the DZL Annual Meeting
- Digital workshop on AI and COVID-19 imaging
- Digital workshop on the “human lung atlas”
- Introduction of a joint imaging project with the German National Cohort (GNC)

of continuously evolving imaging technologies and facilitates their implementation for research and translation. “Imaging” hereby encompasses technologies of various modalities and with different resolutions and dimensions in pre-clinical, translational, and clinical applications. The application of Artificial Intelligence (AI) in the field of imaging has great potential for improving the diagnosis and treatment of patients with lung diseases. So-called deep-learning techniques that enable automated and more complex analyses of data not perceivable to the human eye are at the core of the AI revolution in imaging. Thus, new and complex imaging biomarkers can be generated for the detection, quantification, classification and prognosis of disease outcome. These developments open up new opportunities for the joint analysis of deep-learning-derived imaging biomarkers with clinical, biological and genomic information. The development of the necessary AI algorithms and analysis programs is still at an early stage; however, they will make an important contribution to personalized medicine in the near future.

Scientific Coordinators

Prof. Dr. Peter König (ARCN)

Prof. Dr. Hans-Ulrich Kauczor (TLRC)

Administrative Coordinator

Dr. Birgit Teucher (TLRC)

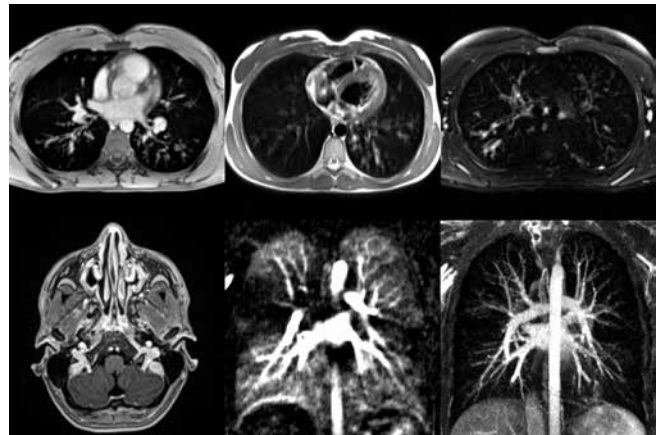
Research Highlight Clinical Imaging 2019

Precise and Radiation-Free: Magnetic Resonance Imaging Gains Ground in Research and Therapy of Lung Diseases

Cystic Fibrosis (CF) and Chronic Obstructive Pulmonary Disease (COPD) are incurable lung diseases characterized by progressive lung damage. Patients are examined regularly to assess disease progression and slow down progression by targeted therapies. Frequent examinations are also common for patients participating in clinical studies to estimate the success of new therapies. Given the high number of examinations that CF and COPD patients experience throughout their lives, it is important to minimize the examination-related burden and apply non-invasive methods whenever possible.

Imaging is the most sensitive non-invasive method used to estimate disease progression in CF and COPD patients. Conventional imaging methods such as X-ray and computed tomography put the patients at risk of accumulating harmful doses of ionizing radiation in the long term. Therefore, DZL scientists from Heidelberg have been working for more than 10 years to establish magnetic resonance imaging (MRI) as a radiation-free method in lung diagnostics. MRI can detect structural damage and functional changes (e.g. perfusion abnormalities) of the lungs. The research team developed various parameters for the analysis of MRI images, which rate the severity of pathological changes to the lung according to a scoring system (MRI score). This scoring system allows for the application of MRI in clinical studies for the development of novel therapies. However, the quality and reliability of MRI-data also had to be tested in numerous studies. The researchers have already demonstrated that MRI data provide information on the severity and individual variation of the disease in CF patients. It can also reflect the success of therapeutic interventions.

In a more recent study, the reproducibility of MRI data was tested further. The study aimed to find out whether two consecutive examinations of the same patient delivered the same results after a short period of time. Therefore, 15 patients with CF and 20 patients with COPD underwent two MRI examinations one month apart. These patients had not experienced any detectable deterioration of their symptoms during this time and were therefore considered clinically stable. On both examination days, lung function tests were also carried out to relate their results to those of the MRI scan. After one month, patients with CF neither showed significant changes in lung function nor in MRI score. MRI-scores of COPD patients showed small changes, which could be attributable to a slight deterioration of the patients' health that was not picked up in the lung function test.



MRI scan of an 18-year-old patient with CF. MRI can detect disease progression in the upper and lower airways during a single examination procedure. Typical changes observed in CF patients include swellings of the nasal mucosa, thickened bronchi and mucus obstruction of the lungs MRI can detect lung dysfunctions and chronic pathological changes in the blood vessels of the lungs.

Thanks to this and further work, the new MRI method is now also applied at different sites to advance research on therapies for lung diseases such as CF and COPD.

Further Information:

- ☑ Wielpütz, MO, Wege, S, Eberhardt, R, Mall, MA, Kauczor, HU, Puderbach, MU, Risse, F, Heussel, CP, Heussel, G. (2019) Midterm Reproducibility of Chest Magnetic Resonance Imaging in Adults with Clinically Stable Cystic Fibrosis and Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 200 (1): 103-107
- ☑ Leutz-Schmidt, P, Stahl, M, Sommerburg, O, Biederer, J, Kauczor, HU, Puderbach, MU, Mall, MA, Wielpütz, MO (2019) Ten years of chest MRI for patients with cystic fibrosis: Translation from the bench to clinical routine. *Radiologe* 59 (Suppl 1): 10-20

Research Highlight Preclinical Imaging 2019

Spectacular Insights into the Lungs of a Mouse Help Develop Nanomedicine. A New Method Allows for Three-Dimensional Imaging of Nanoparticles inside the Lungs of Mice

Nanoparticles can either be harmful or beneficial for humans. The tiny, ultrafine particles have a size of about 1-100 nm, corresponding to the billionth of a meter. They spread easily through the air and can reach regions deep inside the lungs. Inhalation of harmful nanoparticles (e.g. produced during combustion) can promote diseases of the heart and the lungs; however, nanoparticles also have the potential to become valuable tools in the treatment of lung diseases. In the future, they could be used to deliver drugs directly to the site of action inside the airways.

Researchers want to understand how nanoparticles travel through the body to estimate the effects of harmful nanoparticles but also to develop nanomedicine. They often use animal models to track how nanoparticles enter the lung and to estimate how many particles attach at what part of the lungs. Conventional imaging techniques either allow the imaging of

small lung segments with very high resolution, or the imaging of whole lungs with low resolution. However, none of these techniques is suitable to accurately trace the distribution of nanoparticles inside whole lungs.

Therefore, scientists of the CPC-M DZL site have recently developed a novel imaging technique. For the first time, it allows for the imaging of the lungs of mice in three dimensions and the simultaneous location of nanoparticles within the lungs on the cellular level. Fluorescently labeled nanoparticles were delivered into the lungs of anesthetized mice via inhalation of an aerosol or by application of a suspension through a tube (intratracheal instillation). After removal of the lungs, they were prepared with different organic solvents to make the lung tissue more permeable to light and almost transparent. The lungs were then imaged layer by layer using light sheet fluorescence microscopy. The images were assembled to a three-dimensional picture of the lung revealing the entire airway tree from the trachea along the bronchi down to the alveoli or the capillary bed at cellular resolution. As the images were very precise, it was even possible to see differences in the distribution of nanoparticles depending on the way of delivery. The nanoparticles penetrated deeper into the lungs and spread more evenly when they were inhaled rather than delivered by instillation.

This new imaging technique will help advance the development of nanomedicine and find out more about where harmful nanoparticles (including viruses) attach inside the lungs and which cells they can enter.

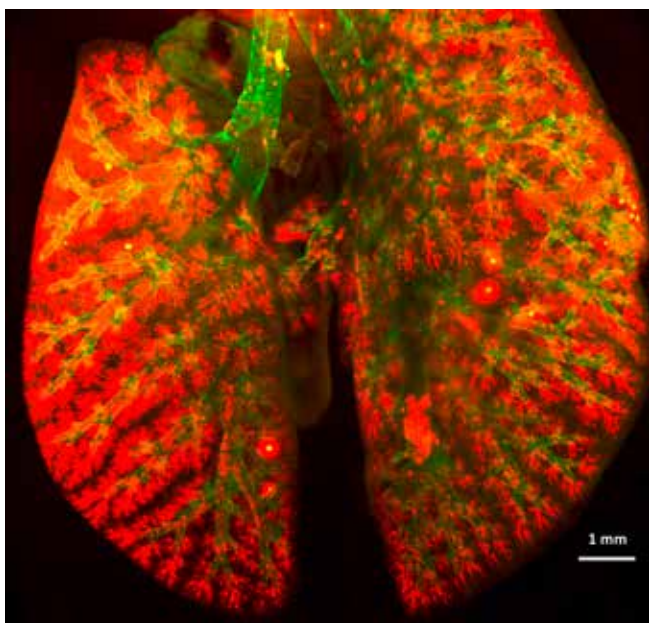


Image of a murine lung after inhalation of fluorescent nanoparticles (red), which were inhaled as aerosol droplets with a size of 3 μm and distributed uniformly throughout the airway tree of the lung (green) even into the most intricate structures of the deep lung (alveolar air sacks). Clearly visible are patterns reminding of the branches of a "Christmas tree" (red) all over the lung but particularly near its rim. These indicate a high deposition of aerosol at the entrance of air sacks (alveolar duct) which has been predicted by computer models but never been observed in such detail before.

Further Information:

✉ Yang L, Feuchtinger A, Möller W, Ding Y, Kutschke D, Möller G, Schittny JC, Burgstaller G, Hofmann W, Stoeger T, Daniel Razansky, Walch A, Schmid O. (2019) Three-Dimensional Quantitative Co-Mapping of Pulmonary Morphology and Nanoparticle Distribution With Cellular Resolution in Nondissected Murine Lungs. *ACS Nano* 13 (2) 1029-1041

DZL Technology Transfer Consortium

Chairmen

Dr. Christian Stein (MD, Ascenion GmbH)

Dr. Peter Stumpf (MD, TransMIT GmbH)

Administrative Coordinator

Dr. Annegret Zurawski (BREATH)

Scientific Advisor

Prof. Dr. Werner Seeger (DZL Chairman)

Efficient and effective exploitation of research results remains a key priority of the DZL. The DZL Technology Transfer Consortium, founded in 2013, is made up of representatives from the technology transfer organizations of all DZL partners as well as representatives from the DZL, among them Prof. Dr. Werner Seeger (DZL Chairman), 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 the 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
Griese M	Diffuse Parenchymal Lung Disease (DPLD)	all	Hydroxychloroquine (HCQ) in pediatric ILD (= children's interstitial lung disease; chILD)
Herold S / Welte T	Pneumonia and Acute Lung Injury	BREATH, UGMLC	GM-CSF Inhalation to improve Host defense and Pulmonary barrier restoration (GI-HOPE) in patients with pneumonia-associated ARDS
Heußel C	Lung Cancer	BREATH, CPC-M, TLRC, UGMLC	Early response capturing in the treatment of adenocarcinoma (ERT-BC)
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
Meister M	Lung Cancer	all	Biomarker exploration in ongoing DZL study "ERT-BC"
Reck M / Ammerpohl O / Barreto G	Lung Cancer	all	Monitoring of patients with NSCLC – 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-M, TLRC, UGMLC	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
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

At the German Center for Lung Research (DZL), more than 260 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 the intensive exchange both between DZL researchers among the sites and of the entire network with external partners is of particular importance. All of them devote themselves to one common goal: to research and combat lung disease to the best of their abilities. 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 500 scientists, physicians, and junior researchers from five sites attended the **8th DZL Annual Meeting on February 7 and 8 at the Rosengarten Mannheim**. This means that the number of participants has risen again this year. Special attention was paid to the outstanding developments in the promotion of junior scientists. In his opening speech, chairman Prof. Dr. Werner Seeger welcomed 20 new Principal Investigators at the DZL; at the same time, he emphasized the positive development in the promotion of junior scientists. **The DZL Academy**, newly established in 2018, which provides students, doctoral candidates, and early postdocs with various options for career enhancement, has already recruited 282 fellows. Around 100 of them attended the first DZL Academy Fellow Reception as part of the Annual Meeting and selected a representative for each site. These representatives were admitted to the DZL Academy Board. During its first year of operation, the DZL Academy has already offered numerous workshops and symposia as well as travel grants. Seeger welcomed the five members of the **International Scientific Advisory Board**, who had come to the event to support the Board of Directors with advice on the further development of the Center. For the first time, the scientists had the opportunity to present their research work not only in the form of posters but also as short teaser talks and participate in the poster prize contest. An independent body then selected the winners, allowing them to present their work to the large audience in a longer presentation on the second day.

On June 5th, Prof. Welte received the internationally leading doctors and researchers in pneumology at the **ERS's annual Presidential Summit**, which took place at Schloss Herrenhausen in Hanover. In addition to 120 scientists, the invited guests included the presidents of the MHH, Prof. Dr. Michael Manns and Dr. Andreas Tecklenburg. ERS, the **European Respiratory Society**, is the world's largest consortium of pulmonary experts, along with its US affiliate ATS. In September 2018, Prof. Dr. Tobias Welte, Clinic Director of Pulmonology of the Hannover Medical School (MHH), took over the presidency of the ERS. In addition to the directors of the various DZL locations, scientists from the DZL were also invited. The friendly family atmosphere of the event was well suited for an exchange with the international colleagues. As a central topic the summit dealt with the **"Unmet Needs in Respiratory Medicine"**. In lectures and small groups this important challenge for the future of lung research was examined from different perspectives. The need to expand collaboration with other medical specialties was identified as the common denominator across the various lung diseases. Pulmonary diseases are often associated with diseases of other organ systems, which should potentially be treated together. The presidential summit set an important impetus for this, which will be further discussed and followed up within the ERS after the summit.

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. DZL scientists and physicians 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 2019 patient fora were organized in collaboration with the DZL at various sites of the Center.

For instance, jointly with the LIS and the German Lung Day (Deutscher Lungentag), the DZL invited interested patients and their families to the **Lung Research Panel** on **March 16, 2019** in **Munich**, the capital of the German state of Bavaria. The theme of the event attended by over 100 people was **“Lung Disease in Children and Adults”**. The event provided patients and their families with the option of asking specific questions, which were answered by qualified scientists and physicians. The event in this format was considered a complete success by everyone.

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 15, 2019** on the margins of the DGP Congress in Munich. 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 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.

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, 29 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 12,000 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 Multi-centre 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 Lungen-

Clinic 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 rarer 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 President of the DGP until March 2019.

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 joint DZG stand was one of the highlights at this year's **125th Annual Meeting of the German Society for Internal Medicine (DGIM) from May 4th to 7th in Wiesbaden**, where the DZG presented their current research results. Despite great advances in medicine, far too many people still suffer from cancer, diabetes, infections, cardiovascular and lung diseases and dementia. The aim of the German Centers for Health Research (DZG) is to bring research results to the patient faster (translation) to improve prevention and treatment of these common diseases. Excellent scientists from university and non-university research institutions work together on an interdisciplinary basis. The DZG were also represented at the annual meeting of the **German Academic International Network (GAIN)** in San Francisco, USA, from 23 to 25 August. The conference is aimed at young German researchers who are currently working in institutions in the USA and Canada and are interested in returning to Germany. Around 400 participants came to find out about the offers of the exhibiting research institutions and universities from Germany at the Talent Fair. In addition to the information stand, the DZG provided a comprehensive overview of the structures, research content and strategies of the DZG. Interested young researchers can benefit from cross-centre cooperation and excellent common infrastructures. The coherent strategy provides long-term prospects.

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 with an information desk and presentations by DZL scientists, as was also the case in 2019 in Madrid. 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. Medical guidelines aim 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 to that, 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.

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 2019

- ✓ Election of Fellow Representatives to the DZL Academy Board
- x Organization of the 1st DZL Academy Fellow Symposium – postponed to 2020
- x Restart of the DZL Mentoring Program – postponed to 2020
- ✓ Funding of mobility grants and training courses
- ✓ Concerted activities with other German DZG centers – Nature Masterclass Workshop
- ✓ Extension of the portfolio of DZL Academy activities to foster DZL-wide research activities driven by early career scientists

Goals for 2020

- Organization of the DZL Academy Fellow Reception on the Eve of the DZL Annual Meeting 2020
- Organization of the 1st DZL Academy Fellow Symposium
- DZL organizes DZG Workshop on "Science Communication"
- Funding of mobility grants and training courses
- Restart of the DZL Mentoring Program
- DZL Academy Fellow Survey on Digital Format Preferences
- DZL Academy goes digital (Twitter, LinkedIn, Training Platform, ...)

DZL Academy Board



Claudia Staab-Weijnitz

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.

Inaugural DZL Academy Fellow Reception 2019

In its first year, the newly established DZL Academy recruited 282 Fellows, who are to benefit from various programs aimed at supporting careers in respiratory research. On the eve of the DZL Annual Meeting 2019, the DZL Academy Board organized a social gathering to formally welcome Fellows to the Academy. Prior to the meeting, Fellows were invited to take part in a survey to make their views and ideas known about what programs may best benefit their careers. With this initiative, the DZL Academy Board wanted to underline its philosophy that the future success of the Academy will very much depend on active Fellow participation in shaping the Academy program. This was further communicated during the reception through the official election of Fellow Representatives from each DZL site to the DZL Academy Board by the Fellow community. Over the next two years, Sebastian Marwitz (ARCN), Svenja Gaedcke (BREATH), Carmela Morrone (CPC-M), Magdalena Szczygieł (TLRC), and Christina Malainou (UGMLC) will add their voice to the DZL Academy Board meetings. After two years on the Board, the opportunity to be actively involved in the strategic development of the Academy will be passed on to a new set of Fellow representatives.

Having completed the more formal aspects of the reception, the evening quickly turned into the kind of social gathering that drives new contacts and networks, which is essential for career development.



The newly elected Academy Fellow Representatives 2019. From left to right: Carmela Morrone (CPC-M), Magdalena Szczygieł (TLRC), Sebastian Marwitz (ARCN), Svenja Gaedcke (BREATH), Christina Malainou (UGMLC).

Scientific Publishing – It Needs a Plan and Special Skills – DZL Early Career Scientists at the Nature Masterclasses Workshop in Berlin

From November 4–5, 2019, six selected early career scientists from the German Center for Lung Research (DZL) participated in the Nature Masterclasses Workshop on Scientific Writing and Publishing in Berlin to improve their writing skills and gain insight into the successful publication process. The workshop was organized by the German Centers for Health Research (DZG) and was the third of its kind. It was open to applications from young scientists of all six DZG. Thus, 36 successful candidates got the opportunity to meet the Chief Editors of Nature Medicine and Nature Metabolism face to face and learn first-hand how to write high-quality publications and how to publish them successfully in top journals. During an interactive exchange with the trainers, participants learned about the aspects editors of top journals look for in papers, found out how to improve their writing style, and gained insights into publication and review processes. During the practical part of the workshop, all participants got the chance to discuss their own abstracts with the editors. All six DZL participants were enthusiastic about the workshop and would highly recommend it to their colleagues. Dr. Natalia El-Merhie, postdoc at the Research Center Borstel and member of the Airway Research Center North, ARCN, summarized: “The workshop was very well structured and the content was excellent – with short lectures, practical sessions, group discussions, and the possibility of one-to-one interaction with the trainers”. Dr. Christina Eichstaedt, scientist at Thoraxclinic Heidelberg, hoped to become more efficient in writing and more successful with submissions to high-ranking journals. She especially appreciated the advice that “by using simple modifications, an abstract and the entire manuscript can turn into a much more interesting read and coherent engaging story.” Agilo Kern, PhD student at Hannover Medical School learned about what really matters when you want your paper to be published in high-ranking journals: “Editors look for papers with findings of broad interest. They should provide novel insights, change the understanding in a field, or open doors to further research”. Dr. Anna Brichkina, scientist at the Institute of Molecular Oncology, Philipps University of Marburg was already able to apply her knowledge gained during the workshop: “Now I know how to



The group of DZL early career scientists together with the DZL Academy representative, Prof. Silke Meiners (second from the left) and trainers Dr. Joao Monteiro (right) and Christoph Schmitt (fifth from the left) at the Nature Masterclasses Workshop in Berlin. (Picture: Natalia El-Merhie).

write a good abstract, and I already managed to improve three of my conference abstracts. I shortened and rephrased them to become more appealing to the reader." On the second day of the workshop, the focus was on editorial and review processes. Dr. Anne-Sophie Lamort, postdoc at the Comprehensive Pneumology Center-Munich (CPC-M), found it useful to learn what defines a good reviewer: "It was interesting to see the revision of a manuscript from a reviewer's perspective. It helped us have a better understanding of their comments and how to anticipate some questions by making small adjustments to our manuscript." Magdalena Szczygieł, PhD student at the German Cancer Research Center (DKFZ) very much appreciated the session on the editorial process and peer review and was surprised to learn that "in about 30% of cases, when a paper is rejected after revision, it is successful on appeal". Furthermore, the very experienced group leader, Prof. Dr. Silke Meiners from CPC-M, appreciated the insiders' view of the publication process in renowned Nature journals. "I realized how highly coherent narrative and compelling reasoning ranks in the decision process for recommending a particular paper for publication. On top of that, a well-composed cover letter is a chance not to be missed to pitch your story to the editors".

The next DZG workshop will take place in spring 2020 at the National Institute for Science Communication (NaWik) in Karlsruhe. Over two and a half days, it will cover the basics of science communication and outreach. More information about the Nature Masterclasses Workshop on Scientific Writing and

Publishing can be found at: <https://masterclasses.nature.com/>.

DZL/ERS Fellowship 2019

Dr. Sebastiano Emanuele Torrisi from the University of Catania, Italy, received a joint fellowship from the European Respiratory Society (ERS) and the DZL to fund his 12-month research visit at the Thoraxklinik, Heidelberg. The funding enabled him to work on a project investigating the impact of comorbidities on diagnosis process, clinical course, treatment management and mortality in patients affected by Chronic Hypersensitivity Pneumonitis and Rheumatoid Arthritis associated Arthritis Interstitial Lung Disease.

DZL Academy – Mobility Grants – Annual Report 2019

In 2019, the DZL Academy provided mobility grants to three Fellows. One grant was used for participation in advanced training at an external institution, while the other two grants were used for training at another DZL site. The aim of the mobility grant program is to increase and tailor the training opportunities of DZL early career scientists to their specific needs. Primarily, the grant supports Fellows who want to visit another DZL-affiliated research group at another DZL site to train in a specific technique or for scientific exchange as part of collaborations. In exceptional cases, visits to non-DZL institutions are also supported. This example shows that mobility grants are an excellent way to promote the exchange of specialist knowledge among DZL sites. This program is planned to be continued for the next funding period as well.

Equal Opportunities and Diversity

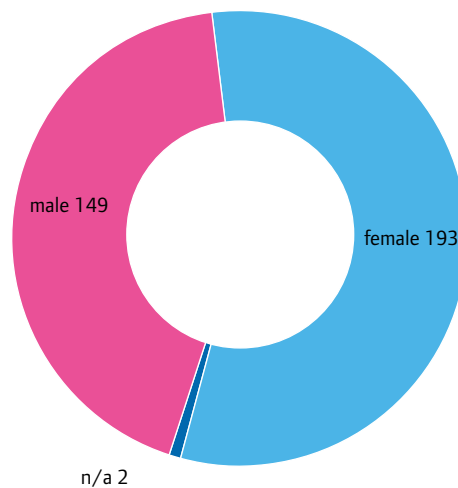
The German Center for Lung Research (DZL) and its Member Institutions are firmly committed to promoting equal opportunities and gender equality of scientists at all DZL sites. For the DZL and its Member Institutions, it goes without saying that nobody may be excluded from a scientific career because of their gender, ethnic origin, age, or medical condition. Equal opportunities and gender equality pay off in many ways: They make it possible to fully exploit the existing innovation and talent potential and increase quality of research due to diversely composed work groups.

In close cooperation with the relevant committees at the corresponding DZL sites, specific measures are implemented to ensure gender equality and equal opportunities.

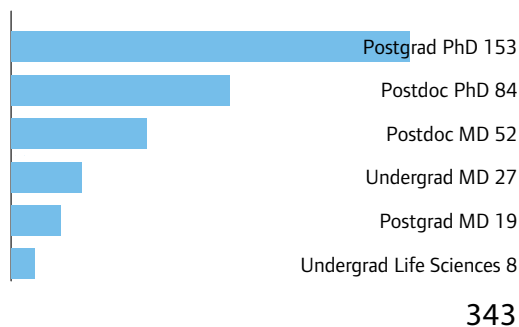
Within the framework of gender-equality programs, priority is placed on the active recruitment of female scientists at every level, from trainee to Scientific Advisory Board, to raise the percentage of female personnel. In particular, the number of

female DZL personnel in leadership positions is to be expanded. Since the founding of the DZL in 2011, the percentage of female Principal Investigators (PIs) has increased from 14% to about 23% in 2019, when the percentage of female personnel funded by the DZL had reached 69%. In 2019, the percentage of female professorships and leaders of junior research groups was about 44%.

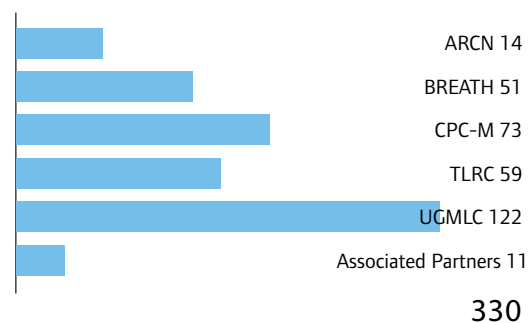
Diversity and equal opportunities among DZL Academy Fellows



Career Status of the DZL Academy Fellows



DZL Academy Fellows according to DZL Site



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.



In 2019, the DZL started to expand its public relations activities. The first step was a redesigned website. With numerous news items about DZL lung research and a great deal of information on the mission and the structure of the DZL, the range of information provided on the DZL web pages received a fresh, modern design. The special homepage section “Publications” shows the latest publications by DZL researchers on a weekly basis. The image film of the research association, which can be found on the DZL website and on YouTube, was also redesigned.

In 2019, the comprehensive DZL Annual Report 2018 was published again in both English and German. Alongside the achievements and highlights of the year 2018, the report presents the numerous successes of the DZL. Furthermore, diverse papers by and with DZL researchers have been published in specialist journals and press articles.

Scientific Conferences and DZL Annual Meeting

In 2019, 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 60th Congress of the German Respiratory Society (DGP), which took place in March 2019 in Munich. The DGP Congress represents the largest scientific forum in the field of respiratory medicine in the German-speaking world.

Public relations activities of the DZL currently involve the DZL's 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) as well as joint activities with the German Lung Information Service (LIS), such as events organized for patients. What is more, in 2019, the joint magazine of the German Centers for Health Research (DZG) “SYNERGIE – Forschen für Gesundheit” (SYNERGY–Research for Health) was published for the first time.

Several times a year, as again in 2019, the DZL also publishes the latest research results, event information, staff matters, and other news about the Center in the “Mitteilungsseiten” (Announcement Pages) in the scientific journal “Pneumologie”.

At the 19th GAIN Conference, which took place in August 2019 in San Francisco, 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 Madrid in September 2019, the DZL was also present with award winners, speakers, and session chairs. In the Congress Area “World Village”, together with other professional associations from all over the world, the DZL provided information about its activities and welcomed ERS (past) President and DZL Board Member Prof. Dr. Tobias Welte to its booth. The DZL's presence at the largest global congress on respira-

tory medicine with more than 22,000 participants from 130 countries around the world plays a vital role in making the DZL more visible, both nationally and internationally.

On the occasion of his ERS presidency, DZL Board Member Prof. Dr. Tobias Welte invited around 120 guests to Schloss Herrenhausen in Hannover in June, where the annual ERS Presidential Summit took place. The central theme of the Summit addressed the “Unmet Needs in Respiratory Medicine”. In presentations and small groups, this important future challenge was examined from different perspectives.

Even in times of modern media, the personal exchange between scientists and the numerous DZL partner institutions at different German sites remains essential. The most important and largest meeting is the DZL Annual Meeting, which takes

place alternately at all sites of the Center. On February 7 and 8, 2019, around 500 scientists, clinicians, and junior scientists discussed project results, strategies, and research objectives at the 8th DZL Annual Meeting in Mannheim. The work groups of the Disease Areas and Platforms also used the opportunity to exchange opinions and benefit from intensive consultation. For the first time, the Imaging Platform entertained the participants with a meet-the-expert session, in which experts provided information on the latest imaging techniques and potential cooperation possibilities in the field of lung research at seven booths with partly fully assembled measuring devices. For the second year in succession, the DZL Academy Fellow Reception took place on the evening before the Annual Meeting, during which junior researchers of all sites had the chance to network and exchange their views and ideas.



DZL at the European Respiratory Society International Congress in Madrid 2019

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 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:

- January 19, 2019 (Augsburg): 20th Patient Lung Forum “COPD and Asthma: Diagnosis, Current Therapeutic Approaches, Living with the Disease”
- March 16, 2019 (Munich): Lung Research Panel for Patients “Lung Disease in Children and Adults”, as part of the DGP Annual Meeting
- October 25, 2019 (Grosshansdorf): 21st Patient Lung Forum “Living with a Lung Disease: Patients Ask – Experts Answer”

Another important part of the contact established with patients (or representatives) are the DZL round-table discussions held since 2016, which allow for the direct exchange on common concerns in 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



Patient Lung Forum 2019 Augsburg

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 ensure better management of their complex chronic conditions. The LIS provides access to science, helping patients to assume 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, 200,000 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 over publications (“Fact Sheets: The Most Important Information in Brief”).



Patient Lung Forum 2019 Grosshansdorf



LID Facebook Followers

At www.lungeninformationsdienst.de, the LIS provides both basic knowledge and new research results to patients, their families, and interested members of the general public in an easily understandable manner. In 2016, the LIS 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 2019, 130 studies had already been recorded on the platform. Key Topics on the LIS Online Portal in 2019: Exercise and Sporting Activities (January), Rare Lung Diseases (February), COPD (March), Diagnosis of Lung Diseases (April), Asthma (May), Patient Training (June), Bronchiectasis (July), Lung Health in Old Age (August), FAQ – Frequently Asked Questions and Answers (September), Clinical Studies (October), and Lung Surgeries (November/December).

From 2011 to 2019, the Lung Information Service published more than 900 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. The LIS also sends out a monthly newsletter to more than 4,500 subscribers. Since 2016, the Lung Information Service has also been

active on social media. It has its own Facebook profile with over 3,600 subscribers and publishes new research information several times per week via the news service Twitter.

The Lung Information Service also distributes its information and material at relevant patient events throughout Germany. In 2019, this included the Annual Meeting of the German Respiratory Society in Munich, the “MünchenerStiftungsFrühling” (Munich Foundation Spring), the Lung Conference Potsdam of the Deutsche PatientenLiga Atemwegserkrankungen e.V., and the Lung Symposium of the COPD - Deutschland e.V. in Hattingen.

The information provided by the Lung Information Service is often picked up on by daily newspapers and other media. In 2019, for example, articles were published in the “Ärztzeitung” (Physicians’ Newspaper), the “Mitteldeutsche Zeitung” (Central German Newspaper), or the “Abendzeitung” (Evening Paper). Since the summer of 2018, the LIS has also been publishing selected contributions 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). DZL scientists also get the chance to issue specialist statements.

Perspectives

With additional services, the Lung Information Service may be able to address new target groups, especially people from educationally disadvantaged backgrounds, more effectively in the future. This might be explanatory videos or podcasts, which will then also 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. Further target groups to which the Lung Information Service wants to give increased attention in the future include general practitioners as well as specialists with deficits in pulmonological know-how, especially in rural areas.

DZL Highlights in 2019

More Informationen can be found at www.dzl.de

Brown Seaweed Extract as a New Therapeutic Approach to Pulmonary Hypertension

DZL researchers demonstrated improvements of experimental Pulmonary Hypertension through the administration of fucoidan, an extract obtained from brown seaweed. PH symptoms were mitigated significantly during the study through the administration of fucoidan, while pulmonary vascular remodeling was also prevented.

Tailor-Made Treatment for Lung Cancer Patients

DZL researchers analyzed tissue samples taken from 3,000 patients with lung cancer during a study using combined DNA/RNA analytics. This diagnostic approach, which goes far beyond current international diagnostic standards and guidelines, helped them detect high-risk patients at an early stage, improve treatment, and gain information on new therapeutic approaches.

An Atlas of the Aging Lungs

DZL researchers have examined the aging process of the lungs at the level of individual cells and evaluated them with the help of artificial intelligence. This resulted in an "Atlas of Aging Lungs", a pioneering project for the Human Cell Atlas (HCA), which is a collection of cellular reference maps that characterize and where each of the thousands of cell types in the human body are found.

DZL Scientist Appointed Heisenberg Professor

DZL scientist Prof. Dr. Bianca Schaub took up a Heisenberg Professorship from the German Research Foundation (DFG). On February 1, 2019, she accepted the W2 Professorship at the Ludwig Maximilian University in Munich with the title "Environment and immunological tolerance development with a focus on the development of allergic diseases".



DZL Researchers Honored with René Baumgart Award

Dr. Astrid Weiß and Moritz Neubauer have been awarded the research prize of the charitable René Baumgart Foundation worth 5,000 euros in prize money. The excellent work of the DZL researchers could be the first step toward the introduction of a new drug into clinical routine in the treatment of patients with PAH, providing them with a perspective for life without pulmonary hypertension.

Targeted Detection of Chronic Lung Disease in Premature Infants

Prematurely born infants often develop a chronic lung disease known as Bronchopulmonary Dysplasia (BPD). To date, it has only been possible to diagnose the condition based on clinical symptoms and with little differentiation. DZL researchers at the Helmholtz Center in Munich and the Medical Center of the University of Munich have therefore developed a new protocol, allowing them to identify premature infants suffering from the disease by magnetic resonance imaging (MRI). →



New Gene-Delivery Systems Raise Hope for Patients with Cystic Fibrosis

DZL researchers developed a new class of non-viral gene-delivery systems, inside which genetic material (DNA or RNA) can be packaged. Through further specific signalling molecules, it is also possible to specify the precise destination of the delivery system, such as certain cells. Initial tests of this gene-therapy approach in an animal model have been successful: By inhalation of the delivery system, the researchers managed to introduce a healthy copy of the CFTR gene into the genome of lung cells.

Pulmonary Hypertension Treated with Cancer Drug

DZL researchers identified a molecular mechanism in Pulmonary Hypertension that controls the disease from the walls of the vessels. With the use of a cancer drug, they managed to stop the pathological remodelling of the blood vessels and to regenerate blood vessels that were already pathologically narrow.

New Insights into Lung Cancer Screening

DZL scientists have investigated in how far computed tomography is suitable for detecting Lung Cancer at a very early stage. The screening slightly but not significantly reduced Lung Cancer mortality in both sexes. In contrast, the researchers observed a significant 69 percent reduction in relative risk among women. The results confirm comparable European studies which provide strong arguments for the introduction of systematic Lung Cancer screening for high-risk groups.

ERS Presidential Summit

DZL Board Member Prof. Dr. Tobias Welte took over the presidency of the ERS. Prof. Welte received the internationally leading doctors and researchers in pneumology at the ERS's annual Presidential Summit, which took place at Schloss Herrenhausen in Hanover. As a central topic the summit dealt with the "Unmet Needs in Respiratory Medicine". The presidential summit set an important impetus for this, which will be further discussed and followed up within the ERS after the summit. →

Balzan Prizes 2019 Awarded in Bern

The DZL was honored with the Balzan Prize for exceptional achievements. The prize is worth 750 000 Swiss Francs. The DZL was awarded for outstanding achievements in the field of „Pathophysiology of respiration: from basic sciences to the bedside“. →



DZL

2019

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.

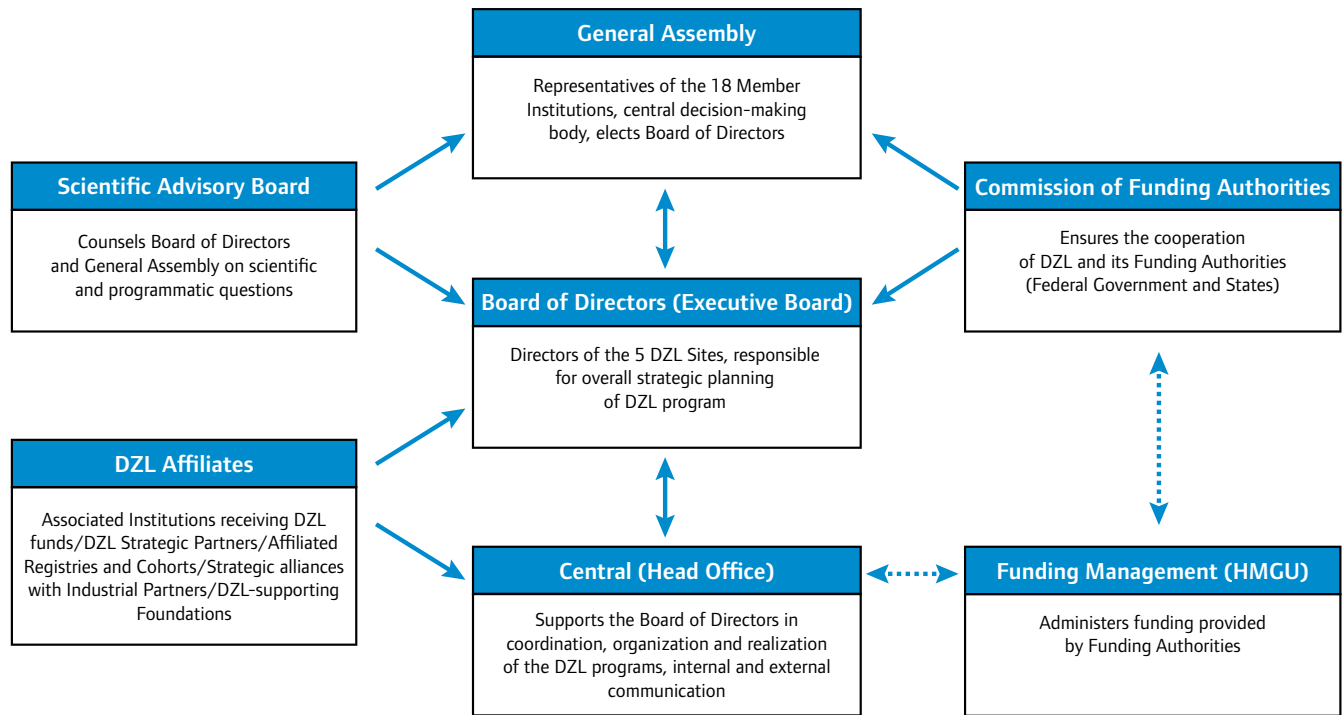
In 2009, the German Center for Neurodegenerative Diseases (DZNE) and the German Center for Diabetes Research (DZD) were founded. In 2011, four additional German Centers for Health Research were established: the German Center for Infection Research (DZIF), the German Center for Cardiovascular Research (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 (GAIN) 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
- Anja Hermann, Management Assistant
- Susanne Klasen, Management Assistant
- Christin Krakau, 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

In 2019, the DZL received special recognition by being honored with the internationally renowned Balzan Prize for the specialist field of “Pathophysiology of respiration: from basic sciences to the bedside”. The DZL received the award for outstanding achievements, which, as the result of innovative research, have provided new therapies and improvements in the quality of life for patients with lung diseases. The Balzan foundation awards four prizes each year to researchers and scientists or artists who have distinguished themselves in their field of activity on an international level. The four subject areas to be honored change from year to year and come from the fields of humanities and social sciences, art, physics, mathematics, natural sciences and medicine. The purpose of the Balzan Prizes is to promote culture and science as well as particularly meritorious initiatives for humanity, peace and fraternity among peoples, regardless of nationality and religious affiliation.

The DZL added its own funds to the prize money of 750,000 Swiss Francs and used it for an interdisciplinary project entitled “Effects of Short and Long Term Exposure to E-Cigarette Va-

pour”. The aim of this project is to examine how the consumption of e-cigarettes affects lung health. The research project is mainly based on projects by young scientists that the DZL would like to particularly support.



Award Winner	Award
Prof. Dr. Werner Seeger (Giessen) Prof. Dr. Klaus F. Rabe (Grosshansdorf) Prof. Dr. Erika von Mutius (München) Prof. Dr. Tobias Welte (Hannover)	Balzan Prize 2019 in the field of “Pathophysiology of respiration: from basic science to bedside”
Prof. Dr. Uwe Haberkorn Heidelberg	A new method for diagnosing lung and other cancers was selected as best clinical publication by the Journal of Nuclear Medicine 2019
Dr. Antje Munder Hanover	Cystic Fibrosis Prize by Mylan Healthcare GmbH
Moritz Neubauer, Dr. Astrid Weiß Giessen	René Baumgart Award
Prof. Dr. Bianca Schaub Munich	DFG* Heisenberg Professorship
Dr. med. Mirjam Stahl Heidelberg/Berlin	DGP** Research Award for the best clinical work
Dr. med. Mirjam Stahl Heidelberg/Berlin	Klosterfrau Research Grant 2019
Wenguang Yin PhD Giessen	DGP** Research Award in the field of fundamental research – best scientific work

Abbreviations:

* Deutsche Forschungsgemeinschaft

** Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin

DZL Member Institutions and Sites



DZL Site Borstel, Lubeck, Kiel, Grosshansdorf Airway Research Center North (ARCN)

Partner Institutions of the Site

- Research Center Borstel – Leibniz Lung Center
- University of Lübeck
- University Hospital Schleswig-Holstein, Lübeck Campus
- University Medical Center Schleswig-Holstein, Kiel Campus
- Christian-Albrecht University Kiel
- LungenClinic Grosshansdorf
- Pulmonary Research Institute at the LungenClinic Grosshansdorf

Prof. Dr. Klaus F. Rabe



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

Contact

DZL Site Coordinator, ARCN:

Dr. Jörn Bullwinkel

E-Mail: j.bullwinkel@lungenclinic.de

Phone: +49 (0)4102 601-2410

Research Profile

Scientists and clinicians of the Airway Research Center North (ARCN) focus on research in the areas of 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 largest North German clinic specializing in lung and airway diseases with more than 13,000 patients treated per year, LungenClinic Grosshansdorf is, together with the University Hospital Schleswig-Holstein (UKSH) and the Medical Clinic Borstel, responsible for clinical and patient-oriented research at 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-Albrecht University Kiel. The 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 LungClinic 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 specialising in pediatric and adult lung medicine work closely together for a better understanding of different disease courses. This crosslink between complementary partners at ARCN aims 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 BREATH DZL Site
- Head of the Department of Respiratory Medicine of Hannover Medical School
- Member of the Internal Advisory Board of the German Center for Infection Research (DZIF)
- President of the European Respiratory Society (ERS) (2018/19)
- President of the German Society for Pneumology and Respiratory Medicine (DGP) (2012–2014)
- President of the German Society for Medical Intensive Care Medicine and Emergency Medicine (DIVI) (2008–2010)
- President of the Paul Ehrlich Society (PEG) (2018–2020)
- Chairman of the Board of Trustees of the CAPNETZ STIFTUNG (foundation)
- Director of the AsCoNet network of excellence
- Member of the reviewing committee for clinical studies of the German Research Foundation (DFG) (since 2016)
- Chief Editor of the European Respiratory Monograph (2009–2015)
- Member of the advisory board of the German Sepsis Society (DSG) (President 2009–2013)
- Spokesman of the DFG review board “Inflammation” (since 2012)

Research Profile

The focus of BREATH is on the translation of findings from basic research into clinical practice, taking into account all topics listed below. This includes carrying out clinical studies of all phases relevant for registration. 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; therefore research in End-Stage Lung Disease is one of the core areas of BREATH. Other closely connected aspects include artificial lung and stem cell research. Extensive preclinical research is conducted in the areas of Infection, Pulmonary Hypertension, Interstitial Lung Diseases and Asthma and Allergies. In the area of basic research, BREATH focuses on the pathobiology of bacterial infections as well as on chronic remodeling processes in the lungs. Further activities aim to better understand the function of the human innate immune system and the control of inflammatory responses in healthy and ill people. 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 field of imaging based on laser techniques. The national research network CAPNETZ aims to improve patient-centered care for adults and children with Community-Acquired Pneumonia (CAP), and is also involved in setting up the PROGNOSIS bronchiectasis registry.

Contact

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

DZL Site Munich

Comprehensive Pneumology Center Munich (CPC-M)

Partner Institutions of the Site

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

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



- Director of the CPC-M DZL Site
- Head of the Department of Asthma and Allergy at Dr. von Hauner Children's Hospital of 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 (DFG)
- Holder of the Cross of Merit of the Federal Republic of Germany
- Fellow of ERS (FERS)

Contact

DZL Site Coordinator, CPC-M:
 Franziska Hauptkorn
 E-Mail: hauptkorn@helmholtz-muenchen.de
 Phone: +49 (0)89 3187-4698

Research Profile

At the Comprehensive Pneumology Center Munich (CPC-M), the Helmholtz Zentrum München – German Research Center for Environmental Health, Ludwig Maximilians University Munich with its University Hospital and the Asklepios Clinic Munich-Gauting have banded together to form one of the largest global centers 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 among 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 German hospitals that specializing 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 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, where 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 regarding 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 TLRC DZL site
- 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

Contact

DZL Site Coordinator, TLRC:

Dr. Birgit Teucher

Email: Birgit.Teucher@med.uni-heidelberg.de

Phone: +49 (0)6221 56 4296

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. Research is focused 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 Asthma and Allergy, 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 UGMLC DZL site
- 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 Institute” (CPI)
- Fellow of ERS (FERS)

Contact

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

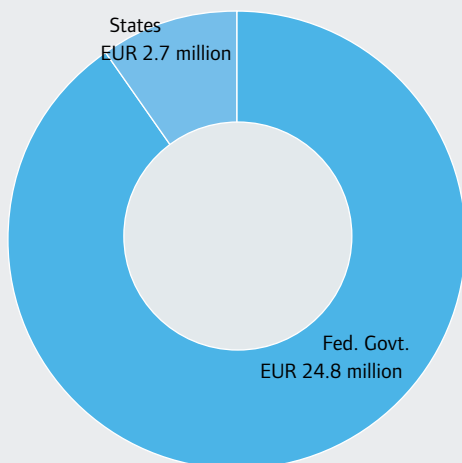
Research Profile

Translational research at the Universities of Giessen and Marburg Lung Center (UGMLC) focuses on lung diseases caused by inflammatory and hyperproliferative processes. This includes research on the antenatal and postnatal impact of environmental factors on the development of Asthma as well as on the development and treatment of Chronic Obstructive Pulmonary Disease (COPD), with a particular focus on the alterations of airways and blood vessels. In the Disease Area Pneumonia and Acute Lung Injury (ALI), UGMLC focuses on the role of innate immunity and inflammatory mechanisms during the acute stage of the disease as well as during resolution and regeneration. Molecular and cellular mechanisms that may help develop efficient regenerative therapies are studied in the Disease Areas Diffuse Parenchymal Lung Disease (DPLD) and Pulmonary Hypertension (PH). The UGMLC partners complement each other through a close interplay of basic research and clinical research, which is based on the cooperation of the Max Planck Institute, the universities and the university hospital. Marburg focuses on the areas of Asthma and COPD, while Giessen's focus is on ALI, DPLD and PH. In principle however, all DZL Disease Areas are represented at UGMLC. In the area of PH, Giessen is regarded as a center of national and international repute. The Max Planck Institute in Bad Nauheim focuses stem cell research, developmental biology and cell signaling pathways. Further synergies result from the cooperation with the other DZL sites as well as with other networks (such as AsCoNet and COSYCONET) and local research consortia like the Excellence Cluster Cardio-Pulmonary Institute (CPI). Within the DZL, UGMLC hosts the DZL Head Office as well as the DZL Biobanking and Data Management Platform.

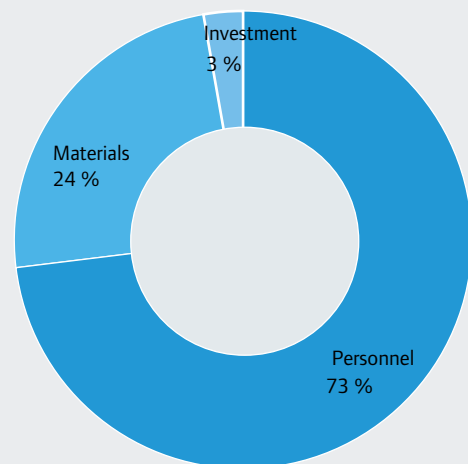
Total Funding and Cost Breakdown 2019

The total funding for the DZL in 2019 was 27.5 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 July 2020)

Total Funding 2019



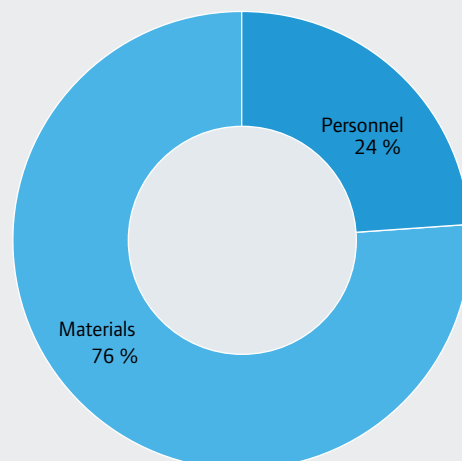
Cost Breakdown: DZL Expenses 2019



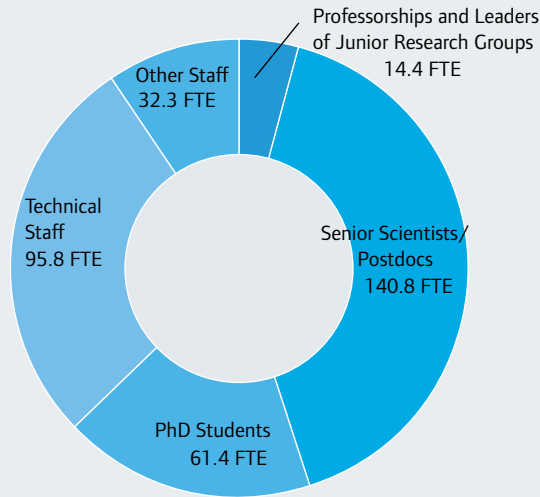
Cost Breakdown: DZL Expenses 2019

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 2019. The 2019 Annual Financial Statement and Year-End Close of the DZL was prepared by the firm Haas & Haas (Giessen)

Cost Breakdown: DZL e. V. Expenses 2019

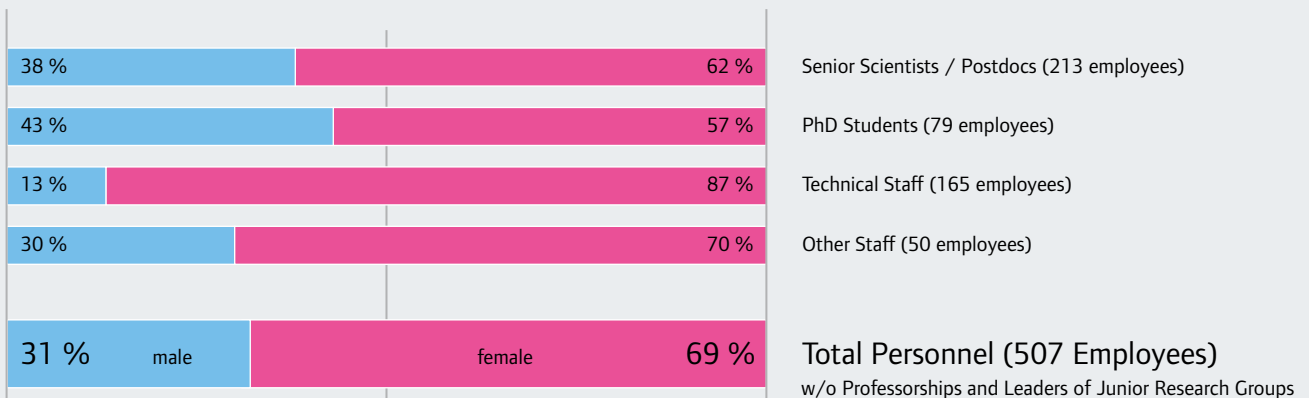


Personnel and Gender Equality 2019

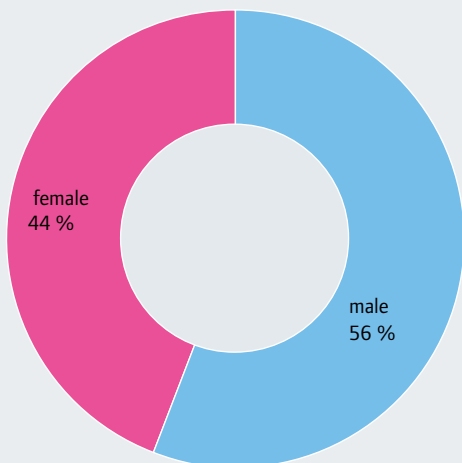


Personnel and Gender Equality 2019

In 2019, 525 employees (344.7 Full-Time Equivalents, FTE) were directly financed with DZL funds across the five partner centers. Of the 525 funded employees, 363 were women (69% of total personnel).



Professorships and Leaders of Junior Research Groups 2019



Professorships and Leaders of Junior Research Groups DZL 2019

In 2019, there were 18 professorships and leaders of junior research groups funded within the DZL, 8 of whom were women (44%).

Masthead

Publisher

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

Head Office

Aulweg 130, 35392 Gießen, Germany

Phone: +49 (0)641 99-46718/-46721, E-Mail: contact@dzl.de, Homepage: www.dzl.de

Board of Directors

Prof. Dr. Werner Seeger (Chairman), Prof. Dr. Hans-Ulrich Kauczor, Prof. Dr. Klaus F. Rabe,
Prof. Dr. Erika von Mutius, Prof. Dr. Tobias Welte

Managing Director

Dr. Christian Kalberlah

Editors/Authors

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

Project Management/Research

Susanne Klasen, Dr. Christian Kalberlah

Photos/Graphics

DZL/DZL partners, unless otherwise specified:

Cover: iStock/damircudic; Page 3: fotolia/Evtstratenko Yuliya; Page 4: E. Shambroom/ARCN; Page 5: iStock/tepic;
Page 6: fotolia/Sergey Nivens; Page 7: E. Shambroom/ARCN serum samples; Page 8: © tiagozr/stock.adobe.com;
Page 10: iStock/Neustockimages; Page 12: Hammerschmidt/Helmholtz Zentrum München; Page 14: iStock/Jan-Otto;
Page 20: iStock/ivanmollov; Page 22: © romaset/stock.adobe.com; Page 23: Mark Wielpütz, Heidelberg;
Page 24: Otmar Schmid, München; Page 26: fotolia/ScienceRF; Page 32: fotolia/alotofpeople; Page 36: Natalia El-Merhie;
Page 40: ©Lungeninformationsdienst – Helmholtz Zentrum München

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.

The DZL is funded by:



Bundesministerium
für Bildung
und Forschung



Baden-Württemberg

MINISTERIUM FÜR WISSENSCHAFT,
FORSCHUNG UND KUNST



Niedersächsisches Ministerium
für Wissenschaft und Kultur

Bayerisches Staatsministerium für
Wissenschaft und Kunst



HESSEN



Hessisches Ministerium
für Wissenschaft und Kunst



Schleswig-Holstein
Ministerium für Bildung,
Wissenschaft und Kultur



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

Head Office

Aulweg 130 | D-35392 Giessen | Germany

contact@dzl.de

www.dzl.de

© August 2020