Deutsches Zentrum für Lungenforschung

DEUTSCHE ZENTREN DER GESUNDHEITSFORSCHUNG

Annual report 2022

Support us now!

Support lung research with your donation: **www.dzl.de/en/donations**
Please feel free to share this link with friends and family too. Thank you!

Table of Contents

Foreword

The Scientific Advisory Board attested an “impressive track-record” to the German Center for Lung Research (DZL) in the written report for the 2022 evaluation. Throughout the year, DZL scientists, doctors, site coordinators, and the DZL Head Office developed the concept for the fourth funding period of the DZL, which is set to begin in 2024. It builds on the results obtained since its establishment in 2011 and incorporates the latest developments in lung research. The presented excellent research concept is capable of further strengthening its position as an internationally leading institution in lung research. In their report, the Scientific Advisory Board calls on the federal and state governments to create a long-term, institutionalized structure with flexible funding allocation for the DZL. Only in this way can the creative spirit within the DZL and its contribution to societal well-being be sustainably secured.

Board (f. l. t. r.): Hans-Ulrich Kauczor, Erika von Mutius, Werner Seeger (Sprecher), Tobias Welte und Klaus Rabe

To ensure the long-term continuation of DZL’s successes, it is also crucial for us to successfully transition to the next generation. The development of responsibilities and forward-looking ‘transition management’ are central tasks that we will tackle. We aim to empower the younger generation of scientists and ensure that their innovative ideas and fresh perspective influence the future of the DZL. In the future, all coordination committees for disease areas and platforms will be supplemented with a member of the DZL Academy. We are particularly pleased that we were able to resume personal exchanges at the 2022 annual meeting in Hanover to further solidify well-established and newly established cross-networking structures. In addition to cross-disciplinary exchanges, the focus is on involving the scientific young talent.

In this report, we guide you through our highlights and progress, our discoveries, and our collaboration in the past year. Read more about where new ideas have taken shape and where we see further potential in the future to jointly explore new avenues in the fight against widespread lung diseases.

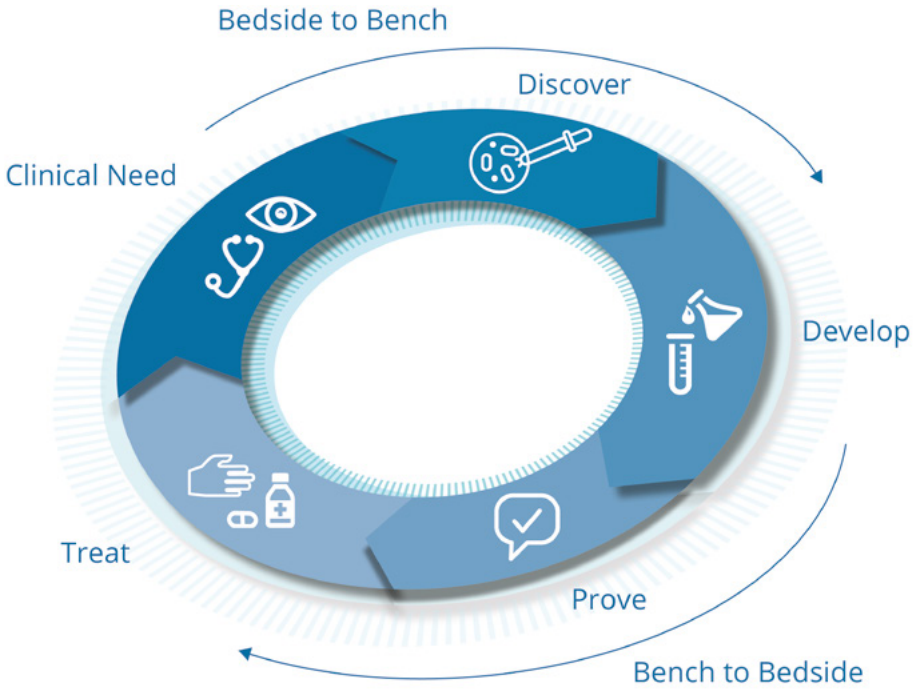
The Board of Directors of the German Center for Lung Research

Translation in the Focus of Research

The German Center for Lung Research (DZL) was founded in autumn 2011 as one of six German Centers for Health Research (DZG). The DZL is funded by the German Federal Ministry of Education and Research (BMBF) and the federal states in which the respective DZL-associated institutions are located. Leading scientists and clinicians in the field of pulmonary research work together in the DZL to develop new innovative therapies for patients with lung diseases.

To date, most respiratory diseases have only therapies that provide symptomatic relief, but no cure. This makes it even more important to develop new approaches and options for disease prevention, diagnosis, and therapy through research into the causes and mechanisms underlying these diseases. Research must address these challenges in a scientifically and structurally coordinated manner to bring together expertise to treat lung diseases more successfully in the future. In the DZL, more than 270 project leaders (principal investigators) and their research groups currently work together to combat lung disease. Twenty-nine leading German research institutions at five DZL locations and other locations of the associated partners cooperate in this work.

Translational research at the DZL aims to better understand the causes of lung diseases and to transfer findings from laboratory research into clinical practice more quickly. The focus is on eight disease areas. Excellent university and non-university institutions work closely together in the DZL for the benefit of patients to rapidly develop new approaches for the treatment of lung diseases. 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 research chain. This close collaboration allows the researchers to conduct large-scale clinical trials with high numbers of participants and access to large amounts of biomaterial and data for medical evaluation. Nevertheless, the path from a discovery in the laboratory to a medical innovation is often a long one. Only a fraction of newly discovered drug candidates reaches the stage where they can be used in patients, and the average development time is 15 years. However, the fact that the DZL's networked translational research brings considerable benefits–both in the long term and in the acute term of a burgeoning pandemic–was already recognized by the German Council of Science and the Humanities in its assessment in 2017, which stated that the DZL "should be further supported without restriction".



Asthma & 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 much alike (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 be successful in tackling this important health problem.

To design personalized treatment approaches for asthma patients, there is urgent need to elucidate the particular molecular mechanisms underlying the various types of asthma. Here, the focus is on environmental factors that influence the immune system favorably or unfavorably (towards asthma). The decoding of corresponding mechanisms and their utilization for individual patients is the goal of the disease area Asthma & Allergy.

Goals Achieved in 2022

- ✅ 3 DZG-overarching publications
- ✅ 19 joint publications of several DZL sites
- ✅ 696 additional medical consultations in the ALLIANCE cohort
- ✅ Further recording of asthma morbidity in the ALLIANCE cohort during various lockdown phases of the SARS-CoV-2 pandemic
- 🟨 Validation of results from basic research on the IL-6 response of the innate immune system in the ALLIANCE cohort (final statistical analysis is in progress, completion expected in 2023)
- 🟨 Molecular characterization of the immune response in trained immunity in primary airway epithelial cells and cell lines (project evaluation delayed due to high variability between samples from different donors, completion expected in 2023)

Goals 2023

- Collaboration with the German Allergy and Asthma Association (DAAB) to include the perspective of patients
- 450 more medical consultations to the ALLIANCE cohort
- 15 joint publications of several DZL sites
- Validation of results from basic research on the IL-6 response of the innate immune system in the ALLIANCE cohort
- Molecular characterization of the immune response in trained immunity in primary airway epithelial cells and cell lines

B Memory Cells Indicate Dysfunction in Small Airways

DZL researchers have found altered numbers of B cells in the blood of individuals with asthma. The results from the ALLIANCE registry could help make it easier to detect inflammation in the small airways in the future.

B cells are a crucial part of the human immune system. Ideally, they recognize invading pathogens and produce specific antibodies to combat them. It was already known from preliminary studies in animal models that asthma affects the B-cell repertoire. Researchers from the ALLIANCE registry have now investigated how this works in patients with asthma using clinical data and blood samples from more than 180 individuals with the disease and healthy control subjects.

The DZL scientists discovered that individuals with severe asthma have fewer immature B cells circulating in their blood than healthy control subjects. Immature B cells are immune cells that have not yet encountered a pathogen. With their specific receptors, they can bind to pathogens, known as antigens, and become activated as a result. This activation is also referred to as the maturation process, which leads to the formation of B memory cells and the production of antibodies. The antibodies produced by B cells bind to pathogens, aiding in their elimination.

The researchers frequently found a specialized type of B cells, known as IgA-positive B memory cells, in those patients who had impaired lung function and damage to the small airways. Immunoglobulin A (IgA) is an antibody class primarily involved in defending against pathogens that enter through mucous membranes. IgA-positive B memory cells were also more common in individuals with asthma who experienced frequent acute disease episodes (exacerbations).

These findings now offer the potential for improved diagnosis of inflammation in the small airways in the future. In this region of the lungs, there are few other options for diagnosis, as sampling from the intricately branched airways is typically infeasible. The biological significance of the identified connection between IgA-positive B memory cells and small airways still needs to be explored. Nevertheless, it could be possible to develop an asthma therapy that leverages this relationship.

Further Information

Habener A, Grychtol R, Gaedcke S, DeLuca D, Dittrich AM, Happle C, Abdo M, Watz H, Pedersen F, König IR, Thiele D, Kopp MV, von Mutius E, Bahmer T, Rabe KF, Meyer-Bahlburg A, Hansen G (2022). IgA(+) memory B cells are significantly increased in patients with asthma and small airways dysfunction. *Eur Respir J* 60(5):2102130.

Scientific Coordinators
Prof. Dr. Susanne Krauss-Etschmann (ARCN),
Prof. Dr. Erika von Mutius (CPC-M)

Administrative Coordinator
Dr. Jörn Bullwinkel (ARCN)

Participating DZL Partner Sites
All

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. Here, we focus on detecting the disease early in order to possibly mitigate its course through early intervention.

Goals Achieved in 2022

- ☑ 22 joint publications of several DZL sites
- ☑ Development of an overarching concept to lung health and early lung injury in chronic lung diseases such as COPD and asthma – Identification of physical activity clusters in COSYCONET using AI analysis in a European comparative project (TOLIFE; Horizon 2021 Health) (Nissen et al., 2023; TOLIFE initiated)
- ☑ Studying the importance of small airways in mild COPD in the CAPTO cohort (Abdo et al., 2022)
- ☑ Studies of macrophage elastase regulation in pulmonary emphysema and chronic bronchitis (Spix et al., 2022)
- ☑ Bi-monthly video conferences for structured coordination

Goals 2023

- 15 joint publications of several DZL sites
- Publication of results on early lung functional changes in smokers ("early COPD") with the Hamburg City Health Study
- Cross-disease area publication on Volatile Organic Compounds with the pediatric part of the ALLIANCE registry (Asthma & Allergy)
- Bi-monthly video conferences for structured coordination

Scientific Coordinators
Prof. Dr. Klaus F. Rabe (ARCN),
Prof. Dr. Claus Vogelmeier (CPC-M)

Administrative Coordinator
Dr. Jörn Bullwinkel (ARCN)

Participating DZL Partner Sites
All

How the Immunoproteasome Sustains Chronic Inflammation in COPD

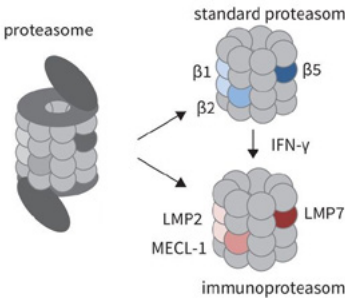
The immunoproteasome influences the persistent inflammation in smokers and those with COPD, making it potentially interesting for the diagnosis and treatment of the lung disease. This is the central finding of a study conducted by DZL researchers published in the European Respiratory Journal.

COPD is characterized by chronic airway inflammation, with immune cells driving this process, making them the focus of many research approaches.

Immune cells have various ways to perceive signals from the environment, determining whether there is any form of threat that needs to be fought off. A relatively unexplored mechanism in this context is the immunoproteasome, a specialized form of proteasome that is unique to immune cells. Proteasomes are present in all cells and act as a sort of cellular shredder, breaking down unneeded cellular proteins, thereby influencing cell function in diverse ways. What sets the immunoproteasome apart is its structural differences from the standard proteasome (see illustration). The immunoproteasome plays a central role in immune cell activity and can enhance inflammatory reactions.

In a study published this year in the European Respiratory Journal, DZL researchers focused on the immunoproteasome, investigating how its function is affected by chronic smoking or severe COPD. They examined immune cells in the blood, known as mononuclear blood cells. They found that the immunoproteasome was more active in both groups compared to control groups, which included non-smokers and individuals without COPD. Additional analyses in patients with severe COPD revealed that the more active the immunoproteasome was, the more impaired lung function was. While this isn't direct proof of a causal relationship between the two measures, the DZL researchers discovered an interesting lead in subsequent experiments, indicating that there might be a connection: When they inhibited the function of the immunoproteasome in blood cells, the release of inflammatory messengers was reduced.

This observation could potentially offer intriguing opportunities for diagnosis and therapy: By measuring immunoproteasome activity, a biomarker indicating the severity of COPD could be developed. In terms of treatment, it might be possible to develop drugs that limit the activity of the immunoproteasome, thereby reducing inflammation. This could alleviate the symptoms and slow the progression of COPD.



The proteasome (on the left) consists of a cap structure and a tube composed of various subunits (spheres). The standard proteasome and the immunoproteasome (on the right) differ in the structure of these subunits. Specifically, β1, β2, and β5 in the standard proteasome are replaced by LMP2, MECL-1, and LMP7 in the immunoproteasome. These distinct subunits cleave protein molecules in different ways, thereby influencing the cell's function. Immunoproteasomes are typically present in immune cells but can also be formed in non-immune cells, especially under the influence of the signaling molecule Interferon Gamma (IFN-γ). This highlights the dynamic nature of these structures and their responsiveness to cellular signals, ultimately impacting cellular function.

Further Information

Kammerl IE, Hardy S, Flexeder C, Urmann A, Peierl J, Wang Y, Vosyka O, Frankenberger M, Milger K, Behr J, Koch A, Merl-Pham J, Hauck SM, Pilette C, Schulz H, Meiners S (2022). Activation of immune cell proteasomes in peripheral blood of smokers and COPD patients: implications for therapy. *Eur Respir J* 59(3):2101798.

Cystic Fibrosis (Mucoviscidosis)

Cystic Fibrosis (CF) is the most common genetically determined, early onset and–even still today–life-limiting form of chronic obstructive lung disease. CF affects approximately one in 2,500 newborns in Germany and leads to severe bronchiectasis. With improvements in symptomatic therapies and standardized CF care, the median survival of patients with CF in Germany has improved to an age of over 40 years. The recent breakthrough in the development of therapies that target the underlying basic defect of CF (so called CFTR modulators) is expected to significantly improve quality of life and life expectancy of patients with CF in the future. Despite the emergence of these new treatments, the disease remains incurable, and important questions regarding the onset and progression of mucus obstruction, inflammation and infection of the airways remain to be resolved. The overall aim of the CF research program is to advance the current understanding of the pathogenesis of CF lung disease and to use this knowledge to improve CF diagnostics, develop more sensitive tools for monitoring of disease activity, and develop novel strategies for effective prevention and therapy of CF lung disease. In addition, results derived from CF research will be used to improve diagnostics and treatment options for patients suffering from other forms of bronchiectasis.

Goals Achieved in 2022

- ✓ Observational study on effects of triple combination therapy with elexacaftor-tezacaftor-ivacaftor on morphological and functional changes in CF lung disease determined by magnetic resonance imaging (MRI) and multiple-breath washout (MBW)
- ✓ Evaluation of effects of elexacaftor-tezacaftor-ivacaftor on Phe508del-CFTR protein maturation, sputum rheology, airway inflammation, and the microbiome
- ✓ Establishment of highly differentiated primary cultures of nasal epithelial cells for precision medicine approaches for patients with rare CFTR genotypes
- ✓ Application of the sweat secretion assay for differential diagnosis of CF and CFTR-associated diseases
- ✓ Preclinical study of the efficacy of a novel mucolytic compound

Goals 2023

- Observational study on long-term response to triple therapy with elexacaftor-tezacaftor-ivacaftor
- Use of CFTR biomarkers for n=1 studies to determine response to CFTR modulator therapy in patients with (ultra) rare CF genotypes
- Assessment of the airway microbiome in chronic airways diseases (CF, asthma, COPD, non-CF bronchiectasis)
- Development of protocols to identify virulence and antimicrobial resistance determinants in the airway metagenome
- Establishment of highly differentiated nasal epithelial cultures for functional characterization of ciliary defects in patients with bronchiectasis and Primary Ciliary Dyskinesia (PCD)

Scientific Coordinators
Prof. Dr. Marcus Mall (Charité/BIH),
Prof. Dr. Burkhard Tümmler (BREATH)

Administrative Coordinator
Dr. Annegret Zurawski (BREATH)

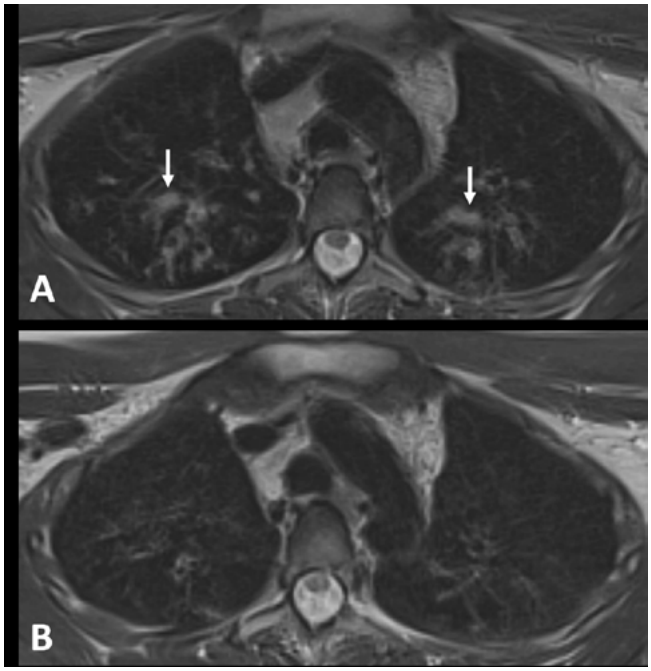
Participating DZL Partner Sites
ARCN, BREATH, TLRC, UGMLC, associated partner site Berlin (Charité/BIH)

The Introduction of a Highly Effective Triple CFTR Modulator Therapy Marks a Decisive Turning Point in the Treatment of the Lungs for Patients with Cystic Fibrosis

DZL researchers were able to show that cystic fibrosis (CF) patients have significantly less mucus in their lungs and their airways are much better ventilated thanks to a new triple therapy consisting of the CFTR modulators elexacaftor, tezacaftor, and ivacaftor (Kaftrio®). They demonstrated this achievement in a prospective observational study at the three DZL sites in Giessen, Hanover, Heidelberg, and the associated partner site in Berlin in a cohort of 91 patients with cystic fibrosis. The scientists used two novel methods, the multiple breath washout, a special lung function measurement that sensitively detects obstruction of the small airways with viscous secretions, and magnetic resonance imaging (MRI) of the lungs. Both methods have been established and harmonized for multicenter studies in recent years in the DZL.

In cystic fibrosis, the gene for an ion channel on the surface of mucosal cells is genetically altered. As a result, the channel which is called Cystic Fibrosis Transmembrane Conductance Regulator (CFTR), does not function at all or only to a limited extent. Recently developed CFTR modulators allow to treat mutations in about 90% of all cystic fibrosis patients. This includes the common F508del-CFTR mutation, which was present at least once in all 91 study participants. Forty-six of the patients studied carried this mutation on both CFTR gene copies, and 45 carried it on only one CFTR gene copy.

The pivotal studies for the new triple therapy previously showed significant improvements of lung function and quality of life by the combination treatment with the three CFTR modulators elexacaftor, tezacaftor, and ivacaftor. However, in these studies, lung function was determined by spirometry, a method that inaccurately reflects the typical functional changes observed in cystic fibrosis. These changes, which are primarily due to obstruction of the small airways by viscous secretions, are assessed more sensitively by multiple breath washout to determine the so-called Lung Clearance Index (LCI). Using multiple breath washout and MRI, the researchers were able to show for the first time that the lungs are much better ventilated down to the smallest airways with the new triple therapy, and that mucus plugging and inflammation-induced thickening of the airway walls were significantly decreased after just three months of therapy. While



Axial T2 propeller MRI images of a 16-year-old female cystic fibrosis patient at baseline (A) and after initiation of elexacaftor/tezacaftor/ivacaftor therapy (B) , showing a marked decrease in mucus plugging (arrows).

the LCI was significantly elevated in most patients before the start of therapy, 40 percent of the patients on therapy had an LCI like that of healthy individuals after three months of therapy.

Currently, the scientists are studying the patients again with the same diagnostic tools, two years after the start of therapy, to determine how the treatment affects the functional and structural changes of the lungs and the progression of the lung disease of patients with cystic fibrosis in the long term.

Further Information

Graeber SY, Renz DM, Stahl M, Pallenberg ST, Sommerburg O, Naehrlich L, Berges J, Dohna M, Ringshausen FC, Doellinger F, Vitzthum C, Röhmel J, Allomba C, Hämmerling S, Barth S, Rückes-Nilges C, Wielpütz MO, Hansen G, Vogel-Claussen J, Tümmler B, Mall MA, Dittrich AM (2022). Effects of Elexacaftor/Tezacaftor/Ivacaftor Therapy on Lung Clearance Index and Magnetic Resonance Imaging in Patients with Cystic Fibrosis and One or Two F508del Alleles. *Am J Respir Crit Care Med* 206(3):311-320.

Pneumonia & 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 attacks (bacteria, viruses, fungi) and non-microbial inflammatory injuries (aspiration, inhalation of toxic gases) may cause Acute Lung Injury with severe respiratory failure. Against the background of the outbreak of the SARS-CoV 2 pandemic, research in this area has gained additional and acute relevance. 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 2022

- ✓ New mechanisms of alveolar-epithelial repair and cellular cross-talk within the stem cell niche: new therapeutic mesenchymal and epithelial targets in severe viral infection including COVID-19
- ✓ Metabolic re-programming of alveolar macrophages (pro-inflammatory to pro-regenerative)
- ✓ Definition of the airway microbiome in pulmonary infection and predictive role in exacerbations of chronic lung disease such as COPD or IPF
- ✓ ESsCOVID study (NCT04576728, use of trimodulin in severe COVID-19 disease, phase IIa) on therapy with inhaled liposomal CsA (L-iCSA) for early COVID-19: start of validation trials for biomarkers (close cooperation with the DZIF)
- ✓ “First data available” from the GI-COVID trial

Goals 2023

- LIGHT (TNFSF14) and TRAIL (TNFSF10) in macrophage-mediated host defense and aberrant tissue remodeling after viral infection
- Innovative human iPSC lung organoids, analysis, and visualization of macrophage-epithelium interactions
- Strategies for therapeutic application, reprogramming of mesenchymal stem cells in virus-induced ARDS in preclinical models
- Transition of “small molecule alpha-toxin inhibitors” to the clinical phase, cooperation DZIF/DZL
- Further development of a biomarker for early sepsis diagnosis (SBM-01), evaluation in clinical cohorts

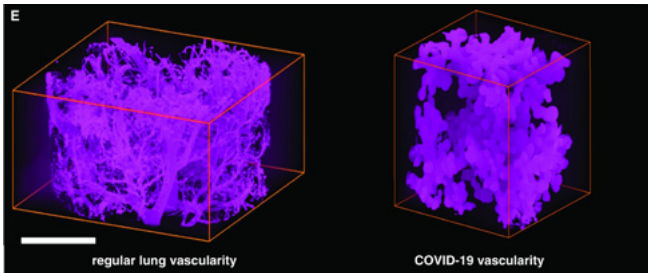
COVID-19 Pneumonia also damages Bronchial Blood Vessels

The severity or morbidity of a COVID-19 infection is largely attributed to pathological changes in pulmonary vessels (inflammation and aberrant vascular development). Most studies conducted on this topic have primarily examined the vessels directly involved in gas exchange.

This study addresses the question of whether the vessels that supply the airways (bronchial circulation) and the so-called vasa vasorum, which are the vessels that connect to the blood vessels themselves, supplying them with oxygen and nutrients, are also affected by similar pathological changes. Lung tissue from individuals who died from COVID-19 was examined using computed tomography angiography and compared to tissue from healthy lung donor organs.

In addition to the known lung tissue damage such as peripheral opacities (radiographically opaque areas), peribronchial fluid and tissue accumulations, and peripheral congestion of larger vessels, a significant expansion and enlargement of peribronchial and perivascular vessels was observed. This redirects blood flow into the bronchial circulation. This process is known as intrapulmonary "shunting" and ensures lung perfusion under various conditions such as inflammation, acute respiratory distress syndrome, or chronic thromboembolism.

In the examined lungs with severe COVID-19 pneumonia, densely packed bundles of vessels were observed in the microvascular architecture of peribronchial vessels, caused by a phenomenon known as intussusceptive angiogenesis (vascular formation by growth into the vessel lumen). Spatial analysis using phase-contrast tomography also revealed numerous peribronchial and perivascular arteriovenous vessel connections, including so-called "lock arteries," and local nodular dilations of vessels.



Three-dimensional representation of the expansion of perivascular vessels in COVID-19 pneumonia

The study provides the first images of the complex three-dimensional phenomenon of bronchiopulmonary vascular remodeling, which can lead to overperfusion with impaired oxygen uptake in severe COVID-19 disease.

It is still unclear what long-term implications this overperfusion due to massive vascular neogenesis and remodeling and the associated impaired gas exchange may have.

This contribution represents an important building block for understanding the complex vascular changes caused by COVID-19 infection.

Further Information

Ackermann M, Tafforeau P, Wagner WL, Walsh CL, Werlein C, Kühnel MP, Länger FP, Disney C, Bodey AJ, Bellier A, Verleden SE, Lee PD, SJ Mentzer Jonigk DD (2022). The Bronchial Circulation in COVID-19 Pneumonia. *Am J Respir Crit Care Med* 205:121-125.

Scientific Coordinators
Prof. Dr. Susanne Herold (UGMLC),
Prof. Dr. Tobias Welte (BREATH)

Administrative Coordinator
Dr. Sylvia Weißmann (UGMLC)

Participating DZL Partner Sites
All

Diffuse Parenchymal Lung Disease (DPLD)

The origin and genetic background of over 200 different diffuse parenchymal (interstitial) lung diseases (DPLD) are diverse. However, the often-severe course of the disease shares similarities: extensive changes in cellular composition and interaction, remodeling of the delicate lung framework, and progressive scarring. In many cases, it leads to lung failure. The causes of most DPLD are unclear, and therefore, only a few limited effective pharmacological treatments, mostly anti-inflammatory and anti-fibrotic approaches, are available. Lung transplantation remains the only curative treatment option.

Within the DZL Disease Area DPLD, internationally renowned basic scientists and clinicians collaborate across locations, utilizing highly specialized techniques, the latest methods, including Artificial Intelligence, and clinically relevant in vitro and in vivo models to investigate DPLD. In carefully defined areas of expertise, new insights are gained into alveolar epithelium injury, epithelial and mesenchymal plasticity, lung framework structure, the role of epithelial stem cell niches, and developmental signaling pathways. New concepts on epigenetic (re)programming and the role of infections and environmental toxins are being developed.

Goals Achieved in 2022

- ✅ Analysis of mechanistic relationships between COVID-19 and DPLD development
- ✅ Development and analysis of overarching models and mechanisms on DPLD from birth to old age
- ✅ Identification of relevant cellular subpopulations and biomarkers using integrative single cell analysis and deep proteomics
- ✅ Establishment of new high-throughput methods to identify therapeutic approaches
- ✅ Expansion of existing registries and their networking within the DZL as well as across the DZL (DZG)

Goals 2023

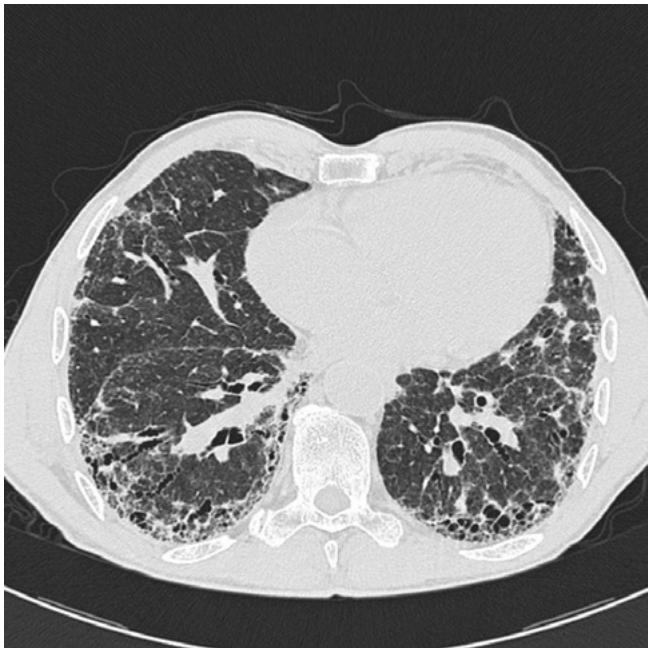
- Studies on the role of inflammatory cells and environmental influences (nanoparticles, viruses) in DPLD, among others, in alveolar organoid models
- Characterization of matrix migration and new dedifferentiation pathways for myofibroblasts
- Spatial analysis of cell circuits and multicellular gene programs, identification of new therapeutic targets, among others, using cultured human lung slices (hPCLS)
- Identification of DPLD endotypes through integrated analysis of disease-characterizing data
- Conducting/advancing planned pre/clinical Phase-II studies

Study on Hydroxychloroquine in chILD: No Significant Effect

Diffuse Parenchymal Lung Diseases (DPLD) are rare diseases. Even rarer but no less dangerous are DPLD in childhood (chILD - childhood interstitial lung diseases). Therefore, it is not surprising that almost all currently used therapeutic approaches for chILD lack support from corresponding controlled studies. The Hydroxychloroquine study, led by clinicians and scientists from several DZL sites, conducted a prospective, multicenter, randomized, double-blind, placebo-controlled parallel-group/cross-over Phase-II study to investigate the important and clinically relevant question of whether Hydroxychloroquine (HCQ) can influence gas exchange (oxygenation), respiratory rate, and/or the need for respiratory support in children with chILD. Secondary study endpoints included health-related quality of life, lung function, and the 6-minute walk distance.

Despite the rarity of chILD, 35 subjects were enrolled in the study, either in a START arm (4 weeks of HCQ or placebo, followed by 4 weeks of HCQ alone, n=26) or a STOP arm (12 weeks of HCQ or placebo, followed by another 12 weeks of placebo alone). The study was concluded after nearly 4 years. No significant effect of HCQ treatment on the primary endpoint or secondary endpoints could be demonstrated. There were no differences in side effects either.

The study's results emphasize how challenging it is to recruit a suitable number of chILD patients for controlled studies even in leading clinical centers. Nevertheless, the study's findings have implications: given the lack of effectiveness of HCQ, the authors suggest a careful reevaluation of HCQ prescriptions in daily practice.



CT image of a lung with interstitial lung disease: clear compaction and scarring in the lung tissue

Further Information

Griese M, Kappler M, Stehling F, Schulze J, Baden W, Koerner-Rettberg C, Carlens J, Prenzel F, Nährlich L, Thalmeier A, Sebah D, Kronfeld K, Rock H, Ruckes C; HCQ-study group; Wetzke M, Seidl E, Schwerk N (2022). Randomized controlled phase 2 trial of hydroxychloroquine in childhood interstitial lung disease. *Orphanet J Rare Dis* 17(1):289.

Scientific Coordinators
Prof. Dr. Andreas Günther (UGMLC),
PD Dr. Anne Hilgendorff (CPC-M)

Administrative Coordinators
Franziska Hauptkorn (CPC-M),
Dr. Jutta Schlegel (UGMLC)

Participating DZL Partner Sites
BREATH, CPC-M, TLRC, UGMLC

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, in particular the pseudo-malignant proliferation of smooth muscle cells in the vessel wall as well as changes to the endothelial cells and fibroblasts. Moreover, a large number of inflammatory cells in the vessel wall contribute to the remodeling process. All this leads to a severe loss of the cross-sectional area of the vessels and an increase in right ventricular afterload. Currently available PH therapy relies on vasodilators that can be administered alone or in combination. While symptomatic relief improves life expectancy, it is not possible to reverse the structural changes and restore the 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 carried out by the PH team.

Goals Achieved in 2022

- ✅ Epigenetic studies of vascular cells in Pulmonary Hypertension
- ✅ Functional and imaging studies of the role of the right heart in various forms of Pulmonary Hypertension
- ✅ Kinase profile from circulating cells from PAH patients
- ✅ Preclinical experiments in different models of PH to investigate the role of new targets
- ✅ Evaluation of databases to validate new risk-adjusted therapy strategies

Goals 2023

- landscape of PH: Experimental studies
- Tyrosine kinase and serine-threonine kinase activity analysis in lung vascular cells and circulating blood mononuclear cells (PBMCs) from patients with Pulmonary Arterial Hypertension (PAH)
- Exploration of key molecular and cellular players driving vascular remodeling in (e)cigarette driven pulmonary vascular remodeling
- Studies in preclinical models of PH to investigate the role of new targets
- Clinical trials addressing the anti-remodeling effects

Molecular “Switch” as a Target for Therapeutic Options in Pulmonary Hypertension?

Pulmonary Hypertension (PH) is a devastating life-threatening disease characterized by progressive and massive remodeling of the pulmonary vasculature turning delicate thin-walled capillaries into thick-walled vessels with reduced inner diameter. Gas exchange is thus drastically impaired, and the right heart challenged with high pressure loads leading to eventual heart failure. Despite breakthrough therapeutical progress – also by DZL scientists and clinicians – there’s still no cure for PH.

The processes of cell proliferation and dysfunctional cell death (apoptosis) regulation associated with PH care also found in cancer. In fact, this study identified the enzyme (peptidylprolyl cis/trans isomerase, NIMA interacting 1) Pin 1, acting as a molecular “switch” in the cell and associated with various forms of cancer. Pin1 changes the spatial conformation of proteins and thereby triggers various signaling pathways, e.g., pathways involved in cell cycle regulation or apoptosis.

The application of juglone (a compound found in walnut trees), which is a specific and irreversible inhibitor of Pin1, was found to reduce pulmonary vascular resistance and remodeling and ameliorate right ventricular function in two experimental models of PH. Pin1 was also found to be overexpressed in tissue samples of PH patients, leading to the assumption that this enzyme also plays a role in the development of this disease. Specific inhibition of this molecular “switch” Pin1, e.g., by juglone, could present a new, attractive therapeutic strategy for treating PH.

The active ingredient Juglone from walnuts: a potential key for the treatment of PH

Further Information

Rai N, Sydykov A, Kojonazarov B, Wilhelm J, Manaud G, Veeroju S, Ruppert C, Perros F, Ghofrani HA, Weissmann N, Seeger W, Schermuly RT, Novoyatleva T (2022). Targeting peptidyl-prolyl isomerase 1 in experimental pulmonary arterial hypertension. *Eur Respir J* 60(2):2101698.

Scientific Coordinators
Prof. Dr. H. Ardeshir Ghofrani (UGMLC),
Prof. Dr. Ralph T. Schermuly (UGMLC)

Administrative Coordinator
Dr. Sylvia Weißmann (UGMLC)

Participating DZL Partner Sites
All

End-Stage Lung Disease

Acute and chronic lung diseases can lead to terminal lung failure. The goal of this DZL area is to enable affected patients to survive with a good quality of life. If ventilation is not sufficient, extracorporeal membrane oxygenation (ECMO) and lung transplantation (LTx) are available. Although the duration of ECMO treatment is still limited, the lung may potentially regenerate during ECMO (e.g., in influenza, COVID-19). In cases of irreversible lung damage, LTx remains the only treatment option, but it is limited to selected patients due to organ shortages and various contraindications (e.g., lung tumors). Furthermore, the long-term prognosis after LTx regarding morbidity and mortality is not satisfactory due to the frequent occurrence of chronic transplant dysfunction (CLAD). Therefore, current research aims to improve the hemocompatibility and biocompatibility of ECMO systems and develop an intracorporeal "biohybrid lung".

In the context of LTx, pre- and post-care are optimized to pursue optimal recipient selection and prevent or detect, classify, and individually treat CLAD. Following recent successes in xenogeneic transplantation of pig hearts, the shortage of organs in the lung field is addressed by establishing xenotransplantation. Additionally, the creation of an artificial lung using tissue engineering is being advanced. This is made possible by significant progress in differentiating human induced pluripotent stem cells (iPS) into various lung cell types. Decellularized lungs are intended to be populated, and new lungs are to be manufactured using 3D printing.

Goals Achieved in 2022

- ✓ Establishment of *ex vivo* therapy for Pulmonary Hypertension using iPS-based endothelial cells
- / CLAD: Cathepsin-B as a biomarker and therapeutic target (Recruitment for clinical study completed)
- / Xenotransplantation: Drug targeting through *ex vivo* lung perfusion (EVLP) (Study in progress, with initial milestones achieved)
- ✓ Biohybrid lung in the large animal model
- ✗ Unilateral lung transplantation for potentially reversible lung disease (planned unilateral lung transplants in cases of lung failure due to COVID-19 infections were unexpectedly not feasible due to the patients' clinical condition)
- ✓ Establishment of an *ex vivo* model for evaluation of pulmonary phage therapy

Goals 2023

- Establishment of an *in vitro* model based on induced pluripotent stem cells for investigating (genetic) respiratory diseases
- Advancement of biohybrid lung technology for application in patients
- Assessment of the risk of Letermovir resistance in difficult-to-treat CMV infection in lung transplant recipients
- Validation of the diagnosis criteria proposed in 2019 for assessing CLAD
- Development of the disease area "End-stage Lung Diseases" towards "Regeneration & Organ Replacement", including the expansion of the circle of involved scientists

Disease Progression of COVID-19 in Lung Transplant Recipients

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2), is currently one of the major threats for immunocompromised individuals. Lung transplant recipients are at particular risk for a worse outcome due to the high dose of immunosuppressive drugs and the lung being the main organ affected by COVID-19.

In a series of publications, DZL scientists contributed to the understanding of COVID-19 in lung transplant recipients during the rapidly evolving pandemic.

Before the use of active immunization and other antiviral measures, 30-day mortality rates for lung transplant recipients with COVID-19 ranged from 30-40%. Later during the pandemic, both hospitalization and mortality rates declined, which has been associated with increasing vaccination rates and the early application of monoclonal antibodies. In an analysis of the pre-delta and delta era, including 1,631 lung transplant recipients from Hanover and Munich DZL sites, the early use of monoclonal antibodies was independently associated with survival after COVID-19, while higher age was associated with COVID-19-related death. However, despite improvements in the outcome, mortality (17%) remained significantly high.

By the end of 2021, the new variant of concern, Omicron (B.1.1.529), became the dominant SARS-CoV-2 strain globally. Concurrently, with the appearance of Omicron, a variety of antiviral treatments became available. A study involving all five DZL sites demonstrated that, in lung transplant recipients, COVID-19 due to Omicron resulted in less severe cases and reduced mortality (6.4%) compared to previous variants. However, COVID-19 remained a significant threat for lung transplant recipients. Vaccination status with a poor response and available early antiviral treatments were not associated with a reduced risk for severe or critical COVID-19. Advanced age and chronic kidney failure were the only risk factors for a worse outcome.

Furthermore, DZL scientists in Hanover and Munich attempted to investigate the role of the recently approved pre-exposure prophylaxis with the SARS-CoV-2-neutralizing monoclonal antibodies tixagevimab and cilgavimab. It has been shown that the number of SARS-CoV-2 infections could be reduced in lung transplant recipients with pre-exposure prophylaxis. Recipients who received pre-exposure prophylaxis had an unfavorable risk profile concerning the severity of COVID-19. However, despite differences, the course and outcome of COVID-19 were similar between the groups, indicating a favorable effect of pre-exposure prophylaxis on the course of COVID-19 in affected individuals.

In summary, this series contributed to a better understanding of risk factors, outcomes, and treatment responses in lung transplant recipients with COVID-19 during the rapidly evolving pandemic.

Further Information

Gottlieb J, Kolditz M, Gade N, Welte T, Kneidinger N (2022). Benefit of monoclonal antibodies in early treatment of COVID-19 after lung transplantation: a retrospective analysis in two centres. *Eur Respir J* 60(1):2200124.

Kneidinger N, Hecker M, Bessa V, Hettich I, Wald A, Wege S, Nolde AB, Oldigs M, Syunyaeva Z, Wilkens H, Gottlieb J (2022). Outcome of lung transplant recipients infected with SARS-CoV-2/Omicron/B.1.1.529: a Nationwide German study. Infection 9:1-9.

Scientific Coordinators
Prof. Dr. Veronika Grau (UGMLC),
Prof. Dr. Dr. Fabio Ius (BREATH)

Administrative Coordinator
Dr. Annegret Zurawski (BREATH)

Participating DZL Partner Sites
BREATH, CPC-M, UGMLC

Lung Cancer

Lung cancer is still being diagnosed too late in many patients, hence prognosis for survival is poor: 40% of all patients with non-small-cell lung cancer (NSCLC) already suffer from metastases at the time of diagnosis. Continuous advances in our knowledge about the genetics and immunology of the tumor have fundamentally expanded the therapeutic landscape with chemotherapy, targeted therapy, and immunotherapy. Alongside the research on genomic changes as the cause of tumor development, our research also targets the tumor microenvironment. Of particular interest are the tumor-infiltrating immune cells and cancer-associated fibroblasts during cancer development and progression. How can we influence the complex interaction between cancer cells and their immediate multicellular microenvironment to prevent tumor growth and spread? Moreover, which measurable parameters, i.e. biomarkers, can predict the onset of cancer, treatment outcomes or resistance? These central questions determine the focus of our research. Among other methods, we use single-cell analysis and proteomics to decipher these complex processes. The technique of proteomics identifies and quantifies the totality of proteins. In combination with the new technology of single-cell analytics, functional and molecular data can now be recorded at the level of individual cells in the complex cell network. Combining all this data, our long-term research goal is to develop individual therapies that are optimized for each patient.

Goals Achieved in 2022

- ✓ Identification of novel molecular risk factors for an activating Exon-20-Insertion of EGFR mutant lung cancer
- ✓ Determination of transcriptome signatures of environmental exposures in lung adenocarcinoma
- ✓ Gain new insights into the cell of origin of ALK-mutated tumors
- ✓ Development of a toolbox for the generation and monitoring of CRISPR-induced lung tumors in preclinical therapeutic trials
- ✓ Exploration of biomarkers for predicting treatment response in pleural mesothelioma

Goals 2023

- Applying spatial biology approaches to interrogate the tumor microenvironment for new prognostic targets and insights on single-cell level
- Identification of molecular and cellular factors of therapy resistance in ALK-mutated tumor cells
- Single-cell level transcriptome analysis in circulating tumor cells in NSCLC
- Investigation of regional immune cell populations and immune biomarkers in tumor and lymph nodes
- Optimization of methods and processes for the detection of EGFR mutations

Scientific Coordinators
Prof. Dr. Rajkumar Savai (UGMLC),
Prof. Dr. Michael Thomas (TLRC)

Administrative Coordinator
Dr. Birgit Teucher (TLRC)

Participating DZL Partner Sites
All

Lung Cancer Research: From the Lab to the Clinic

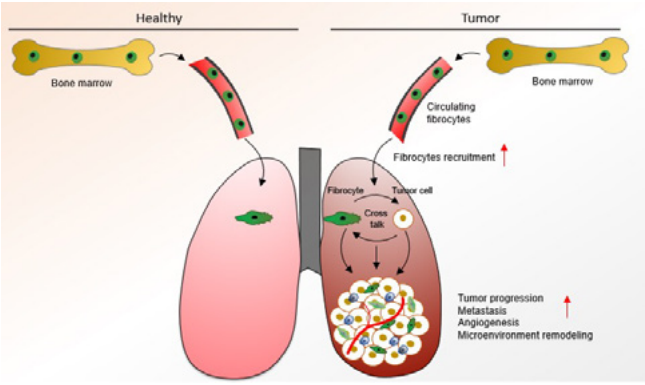
From all the research published by DZL lung cancer scientists last year, three papers were selected for this report that are typical of insights gained into tumor development (basic science), innovative method development for cancer research (translation), and a new approach to phenotyping that is meant to support physicians in treatment selection (clinical science).

Unravelling the tumor microenvironment: Fibrocytes boost lung tumor development

To gain insights into the role fibrocytes play in the development of lung tumors, DZL-scientists from the Savai lab (UGMLC) used a genetically engineered mouse model to study the effect of selective fibrocyte depletion on the tumor. Compared to the control group, the lung tumors in mice without fibrocytes were much smaller. In further experiments, fibrocytes were shown to interact with tumor cells, to reduce the activity of macrophages (white blood cells of the immune system) in tissue and to support the formation of new blood vessels. Responsible for the cell-to-cell communication and effects observed is the messenger compound endothelin-1. In contrast, the blockade of endothelin-1 receptor in both the mouse model and cell culture successfully suppressed tumor development. If further studies confirm the blockade of endothelin-1 receptor as a therapeutic concept, this may lead to the development of new targeted medications.

Preclinical milestone: new method spares animals in cancer research

For many years, the Stiewe Lab (UGMLC) and partners have been researching methods to reduce, refine or replace animal experiments in cancer research. Instead of breeding genetically modified mice to induce tumor growth, the new method induces tumorigenic mutations in adult mice. The research team used CRISPR technology to directly induce multiple defined tumorigenic mutations into living mice. This method allows for novel cancer therapeutics to be tested without the laborious breeding of genetically modified animals that may not have the desired complex genotype, thereby reducing the number of animals for each experiment. In addition, this method models the natural course of tumorigenesis in humans more closely in that the underlying genetic mutation is not inherited but acquired during one's lifetime.



Schematic representation of interaction between fibrocytes and tumor cells within the tumor microenvironment

Precision medicine: new phenotypes for predicting the course of lung cancer

Removing the tumor surgically is the first choice of treatment for lung cancer diagnosed at an early stage. However, overall survival is highly variable after curative resection of the tumor. On the trail of identifying biomarkers for prognosis and response to therapy, scientists from the Stathopoulos lab (CPC-M) assessed the tumor tissue from 200 lung cancer patients for seven characteristic histopathological hallmarks and functions of cells that are usually acquired as these cells progress to turning cancerous. Two groups were identified with a distinctly different prognosis for overall survival: the proliferative and the apoptotic phenotype. Stratification of patients by these phenotypes may significantly impact the clinical management of these patients, including the decision on therapeutic treatment.

Further Information

Weigert A et al. (2022). Fibrocytes boost tumor-supportive phenotypic switches in the lung cancer niche via the endothelin system. *Nat Commun* 13(1):6078.

Merle N et al. (2022). Monitoring autochthonous lung tumors induced by somatic CRISPR gene editing in mice using a secreted luciferase. *Molecular Cancer* 21(1):191.

Lamort AS et al. (2022). Prognostic phenotypes of early-stage lung adenocarcinoma. *Eur Respir J* 60(1):2101674.

Biobanking & Data Management Platform

The goal of the DZL Biobanking & Data Management platform is the Standard Operating Procedure (SOP)-based acquisition, processing, collection, and storage of biomaterials, along with the collection of associated clinical data from various pulmonary disease areas, while adhering to legal standards. The platform aims to provide researchers within the DZL and external collaborators with easy and compliant access to biomaterial and data. In terms of quality management, the harmonization of informed consent documents, data protection concepts, standardized workflows regarding quality control, and data management is a central concern for all DZL sites.

Goals Achieved in 2022

- ✓ Biobanking: Prospective collection of biosamples and associated clinical data (permanent goal)
- / Creation of disease-specific core datasets for all Disease Areas in coordination with DA coordinators and specialists
- / Definition of a DZL core dataset
- / Creation and application of rules to improve data quality (validity, plausibility, completeness)
- ✓ Networking activities with other DZG in the field of biobanking/data management (permanent goal)

Goals 2023

- Prospective collection of biosamples and associated clinical data, along with data integration and update of retrospective and prospective data collections
- Network activities with other DZG and initiatives in the field of biobanking/data management (e.g., TMF, GBA/GBN, MII)
- Further development of rules to improve data quality, implementation of regular data quality reports for local data managers for integrated datasets
- Finalization of the DZL core dataset and disease-specific core datasets for all disease areas
- Update of the DZL Data Warehouse to the latest software versions

Scientific Coordinators
PD Dr. Karoline Gaede (ARCN),
Prof. Dr. Andreas Günther (UGMLC)

Administrative Coordinators
Dr. Jutta Schlegel (UGMLC),
Dr. Sylvia Weißmann (UGMLC)

Central Biobanking Management
Dr. Clemens Ruppert (UGMLC)

Central Data Management
Raphael Majeed (UGMLC)

The Epigenetic Reactivation of Transcription Factors Involved in Fetal Lung Development Contributes to Vascular Remodeling in Pulmonary Hypertension

Pulmonary Hypertension (PH) is a severe lung disease caused by changes in the blood vessels of the lungs. Cells from all layers of the vessel walls are affected, contributing to abnormal thickening of the lung vessels, leading to an increase in pressure in the pulmonary circulation. Currently available therapeutic approaches are based on vasodilatory medications, providing symptomatic relief, and improving life expectancy. However, these methods do not reverse structural changes or restore the functional integrity of lung vessels.

Soni Savai Pullamsetti's research group (Chelladurai and colleagues), utilized isolated cells and precision-cut lung slices (PCLS) from the DZL Biobank to investigate molecular connections between transcription factors, transcription co-activators, and changes in chromatin status during vascular remodeling in patients with PH. They observed that genes in the cells of PH patients are activated differently than in healthy individuals, and there are alterations in chromatin structure influencing gene activity.

Certain transcription factors, crucial in the early phase of lung development and usually suppressed after birth, were found to be activated in PH patients. Experiments with cells from the lungs of PH patients demonstrated that turning off or inhibiting these factors led to a reduction in symptoms of PH. Pharmacological inhibition of specific molecules reduced vascular remodeling. Similar results were observed in animal models.

The researchers gained crucial insights using samples from the DZL Biobank. The findings indicate that in PH, there is an epigenetic reactivation of specific transcription factors. Controlling this change could be a potential approach for future therapies.

Further Information

Chelladurai P, Kuenne C, Bourgeois A, Günther S, Valasarajan C, Cherian AV, Rottier RJ, Romanet C, Weigert A, Boucherat O, Eichstaedt CA, Ruppert C, Guenther A, Braun T, Looso M, Savai R, Seeger W, Bauer UM, Bonnet S, Pullamsetti SS (2022). Epigenetic reactivation of transcriptional programs orchestrating fetal lung development in human pulmonary hypertension. *Sci Transl Med* 14(648):eabe5407.

Imaging Platform

The imaging community consists of radiologists, pre-clinical scientists, IT experts, researchers in imaging physics, image analysis, machine learning, and other disciplines that work in close collaboration with each other. In radiology and microscopy, a broad spectrum of innovative imaging techniques is used to gain new insights into the development and evolution of lung diseases, to test therapeutic efficacy and to support the development process of new drugs. “Imaging” in this context is understood as the combination of imaging techniques of different modalities (magnetic resonance, X-ray, computed tomography, ultrasound, light and electron microscopy, nuclear physics etc.) of different resolutions and different scales in pre-clinical, translational, and clinical settings to inform about anatomical structures and physiological events.Artificial Intelligence (AI) in imaging has the potential to improve the diagnosis and treatment of patients with lung diseases and to advance pre-clinical research. An important role is played by so-called deep learning methods, which are designed to enable automated and deeper analysis of image information that is not accessible to the human eye. Thus, new and complex imaging biomarkers can be generated for the detection, quantification, classification, and progression prediction of lung diseases. The development of the necessary AI algorithms and analysis programs is progressing fast, and they will make an important contribution to personalized medicine in the near future.

Goals Achieved in 2022

- ✓ Examination of damaged lung structures for better detection of characteristic change processes
- ✓ Continuation of the imaging portfolio for clinical studies
- ✓ Development and translation of novel imaging biomarkers
- ✓ Further development of modern imaging technologies, computer-aided diagnosis and artificial intelligence
- ✓ DZL-wide imaging workshop for interdisciplinary exchange

Goals 2023

- All of the above work packages will be pursued as goals for 2023

Scientific Coordinators
Prof. Dr. Hans-Ulrich Kauczor (TLRC),
Prof. Dr. Peter König (ARCN)

Administrative Coordinator
Dr. Birgit Teucher (TLRC)

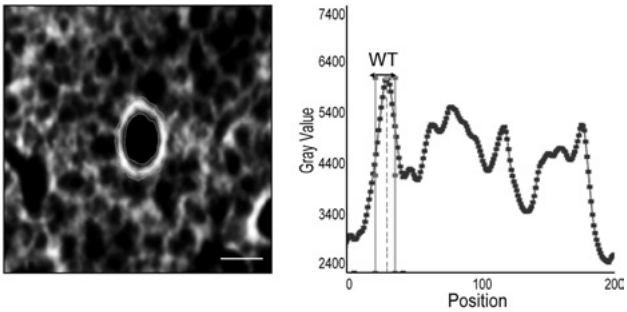
Preclinical Lung Imaging Model for Drug Testing

DZL scientists report another success in lung imaging using three-dimensional micro-computed tomography (micro-CT) to quantify lung parameters in a preclinical model.

Cystic fibrosis and chronic obstructive pulmonary disease (COPD) belong to a spectrum of lung diseases that permanently damage the structure of the airways (bronchi). One major contributing factor is viscous mucus, which provides a good breeding ground for bacteria and other germs, fostering chronic inflammation of the airways. Recurrent lung infections thus carry a high risk of progressive and permanent structural damage to the bronchial walls. Research into novel therapeutics that can reduce or mitigate this damage needs sensitive preclinical models to support rapid transfer of potential drugs to the clinic.

The present study used mouse lungs to quantify for the first time the onset and progression of disease-induced structural changes using micro-CT. The researchers used a genetically modified mouse model that does not secrete the messenger substance (neutrophil elastase) produced by inflammatory processes and thus prevents or reduces tissue damage. When compared to mice that were not genetically altered and therefore had the disease-related structural damage to the lung tissue, it was possible to quantify the disease-related effect on the reduction of airway surface area, changes in lung volume as well as the proportion of oxygen in lung tissue, and the size of the lung volume of the small airways.

Within the framework of the project, a number of new mathematical methods for image analysis were developed or optimized. The structural changes that were previously determined with volume computed tomography and histology confirm the results of this study, but are far surpassed in their precision by the higher resolution of micro-CT. Further research is underway to reduce radiation exposure necessary for monitoring the course of therapy. Based on these methodological advances, the preclinical model developed here is suitable for the investigation of novel therapeutics.



Analysis of the wall thickness of the small airways (distal bronchi), which allows quantification of disease-related structural changes.
Left: A distal bronchus was manually selected for quantitative analysis. The edges of the inner and outer bronchial walls (solid lines) were detected using YACTA software.
Right: The gray value profile of a trajectory from the airway center across the bronchial wall into the lung parenchyma is displayed. Bronchus wall thickness (WT) was calculated using the full width at half maximum (FWHM) method.

The study was conducted by DZL researchers from the Translational Lung Research Center Heidelberg (TLRC) and Charité University Medicine, in collaboration with colleagues from Mainz University Medicine and Shanghai Jiao Tong University.

Further Information

Zhu L, Duerr J, Zhou-Suckow Z, Wagner W, Weinheimer O, Salomon J, Leitz D, Konietzke P, Yu H, Ackermann M, Stiller W, Kauczor HU, Mall MA, Wielpütz MO (2022). µCT to quantify muco-obstructive lung disease and effects of neutrophil elastase knockout in mice. *Am J Physiol Lung Cell Mol Physiol* 322(3): L401-L411.

SARS-CoV-2 infection during pregnancy may impair prenatal lung development

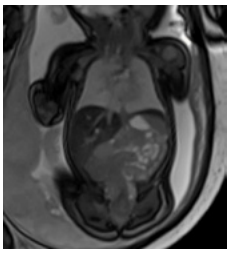
The impact of coronavirus on the unborn child was investigated first by researchers at the DZL Munich site (CPC-M) using prenatal magnetic resonance imaging (MRI). Lung volume was found to be significantly reduced in fetuses whose mothers had experienced an uncomplicated SARS-CoV-2 infection during pregnancy. The study included 34 pregnant women with mild SARS-CoV-2 symptoms that had acquired an infection with the alpha variant at varying time points during pregnancy, before any vaccine was available.

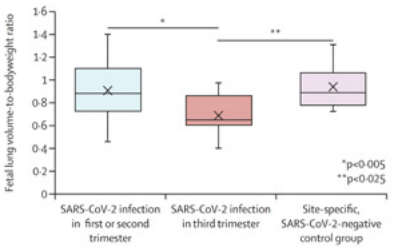
Magnetic resonance imaging as prenatal diagnostic tool for lung development

The lungs of the fetuses were measured by prenatal MRI between weeks 24 and 40 of gestation. Using this non-invasive imaging technique, lung volume can be determined as early as in week 18 of pregnancy. One particular challenge for imaging the fetal lung is the very small size of the structures of interest, which therefore requires a sufficiently high spatial image resolution. The acquisition time of individual sequences, however, must be kept as short as possible since the fetus is moving and–unlike adult patients–cannot be instructed to remain still during image acquisition. For clinical and scientific evaluation, sequences had to be repeated several times in some cases, until they were free of movement artefacts. The highly dynamic nature of MRI-morphologic representation of lung structures during the course of gestation is another distinctive aspect of fetal lung imaging. Accurate knowledge of changes associated with developmental physiology are essential for MRI image interpretation.

Reduced prenatal lung volume

In comparison with a reference cohort, the fetuses of Corona-infected pregnant women had a reduced lung volume. The impact was particularly pronounced in the last trimester of pregnancy, being on average 69% of the volume that is associated with normal lung development.





Left: Coronal view of the healthy fetal lung at 28 gestational weeks. The T2-weighted signal of the fetal lung increases during pregnancy with increasing volume of the amniotic fluid-filled–later air-filled–spaces of the lung. This increase is particularly pronounced in the 3rd trimester, when the greatest increase in volume occurs in the saccular stage of lung development.

Right: Significant reduction of normalized fetal lung volume (normalized by estimated fetal body weight and expressed as percentage of 50th percentile of reference values) with infection time-point in the 3rd trimester (red) vs. 1st and 2nd trimester (blue) and versus a site-specific SARS-CoV-2- control group (purple).

Particularly in the last trimester, the fetal lung undergoes a crucial transformation due to the maturation of cells that are important for gas exchange. Hence, a possible explanation for this phenomenon could be the transfer of the virus across the placenta into the amniotic fluid, and from there into the fetal lung, where contact of these cells with the virus could have affected lung development.

The newborns were predominantly of normal weight and did not suffer from any respiratory distress or other disorders. The extent to which the reduced fetal lung volume may impact on further development will be investigated in follow-up studies in year two and five after birth. In addition, a different follow-up study will investigate the impact of a mild infection with the Omicron variant on fetal lung development in vaccinated pregnant women.

Further Information

Stoecklein S, Koliogiannis V, Prester T, Kolben T, Jegen M, Hübener C, Hasbargen U, Flemmer A, Dietrich O, Schinner R, Dinkel J, Fink N, Muenchhoff M, Hintz S, Delius M, Mahner S, Ricke J, Hilgendorff A (2022). Effects of SARS-CoV-2 on prenatal lung growth assessed by fetal MRI. *Lancet Respir Med* 10(4):e36-e37.

DZL Technology Transfer Consortium

Chairmen
Dr. Christian Stein
(Managing Director, Ascenion GmbH),
Dr. Peter Stumpf
(Managing Director, TransMIT GmbH)

Administrative Coordinator
Franziska Hauptkorn (CPC-M)

Scientific Advisor
Prof. Dr. Werner Seeger (DZL Chairman)

The DZL Technology Transfer Consortium supports DZL scientists in the systematic and effective utilization of their research results. It comprises representatives from the technology transfer organizations of all DZL partner institutions, along with representatives from DZL, including Prof. Dr. Werner Seeger (Chairman of the DZL Board), who serves as a scientific advisor, and Franziska Hauptkorn, Coordinator of the DZL site CPC-M (Munich).

In preparation for the DZL Annual Meeting in 2022, the consortium reviewed more than 300 abstracts for patent-relevant content.

The consortium provides DZL members with various services, including:

- Abstract screening before DZL meetings
- Abstract screening "hotline" for inquiries as needed
- Verification of content in exploitation agreements
- Target consultation and advice to prepare scientists for scientific evaluations by the Federal Institute for Drugs and Medical Devices (BfArM) to prevent potential procedural errors in advance

The technology transfer consortium of the DZL comprises the following institutions:

ascenion
EMBLEM TECHNOLOGY TRANSFER
Max-Planck-Innovation
dkfz. DEUTSCHES KREBSFORSCHUNGSZENTRUM IN DER HELMHOLTZ-GEMEINSCHAFT
technology transfer heidelberg
CAU Kiel University Christian-Albrechts-Universität zu Kiel
Fraunhofer
PVA SH GmbH
TransMIT Gesellschaft für Technologietransfer mbH

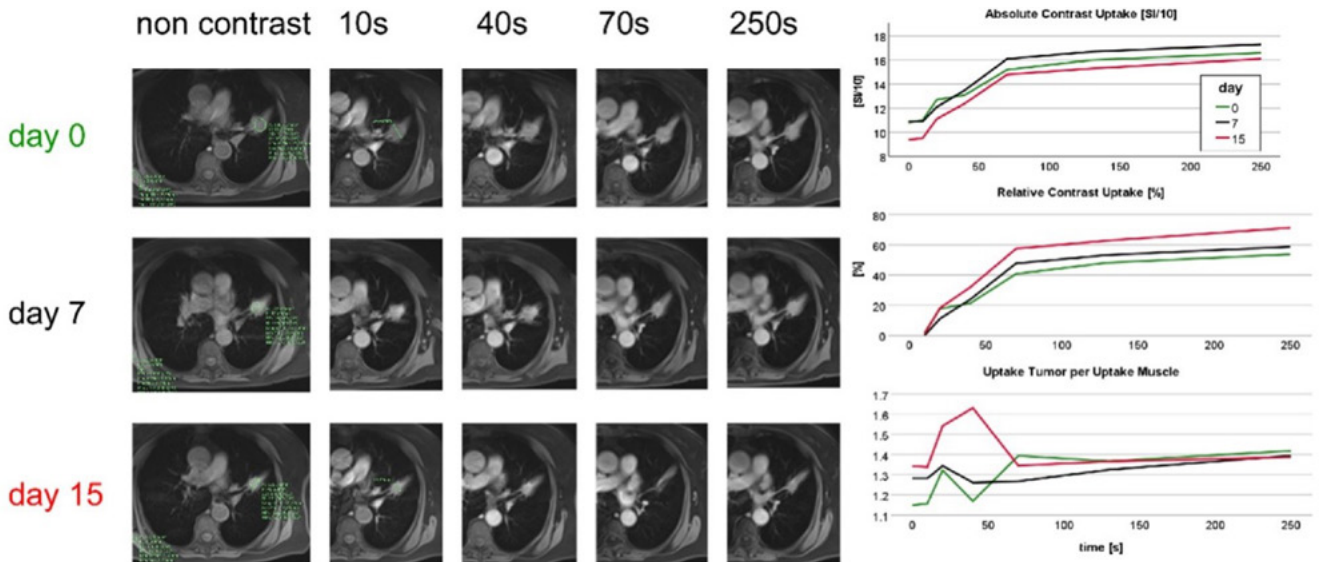
Clinical Trial Board and Clinical Studies in the DZL

Each year, DZL allocates a portion of its budget for innovative clinical studies initiated by DZL scientists ("Investigator Initiated Trials"). This funding allows researchers to respond to the latest developments in their field and quickly advance them for the benefit of patients. These funds are meant as seed capital to enable the rapid transfer of the latest findings into "first in human" investigations. In 2022, the total funding volume for ongoing studies amounted to €1.53 million. Additionally, funding for three more studies was approved, with a total funding volume of €728,000 until the end of 2023. In a second funding line for the preparation and submission of proposals for clinical studies, two such proposals were approved in the reporting year, each amounting to €30,000. The goal of this funding line is to use the completed full proposals for submissions to DZL as well as other funding agencies such as the DFG or BMBF. In addition to studies financed by DZL, DZL scientists are involved in over 250 clinical studies on novel diagnostic and therapeutic approaches to lung diseases. Most of these studies are conducted in collaboration with the pharmaceutical industry and are financed by them.

Lung Adenocarcinoma Therapy Guidance: Can DCE-MRI Make a Difference?

The clinical setting still lags an established method that allows to detect an early response to therapy within the first days and/or weeks after initiation of systemic therapy in the treatment of non-small cell lung cancer (NSCLC). For patient management, however, the early response detection is extremely important for minimizing the toxic burden and side effects associated with various therapies. A DZL-funded clinical trial has now established a non-invasive imaging method to better predict response to therapy and prognosis for patients with adenocarcinoma of the lung, shortly after initiation of systemic treatment.

Led by the DZL Heidelberg-site, the study examined 98 NSCLC adenocarcinoma patients treated with either tyrosine kinase inhibitors (46 patients; TKI) or platinum-based chemotherapy (52 patients; PBC) using dynamic con-



81-year-old female never smoker with adeno carcinoma in the left upper lobe (T4N1M1) who responded to TKI treatment with a progression free survival of 234 days (progression with liver metastases), and an overall survival of 1182 days. The relatively long progression free and overall survival is associated with minimal increase of contrast enhancement.

trast-enhanced magnetic resonance imaging (DCE-MRI) and diffusion-weighted imaging (DWI-MRI). As an alternative to computed tomography (CT), DCE-MRI does not expose patients to radiation, making it particularly suitable for therapy monitoring. DCE-MRI scans were performed immediately before therapy initiation, as well as the day after (PBC) or one week (TKI) later. The study inclusion criteria were kept intentionally broad to reflect the reality of everyday clinical practice. To determine treatment response and for prognosis of disease progression, patients were followed-up for an average of 825 days.

The more contrast agent the tumor had taken up before and in the early phase after therapy initiation, the better the response to therapy as well as progression-free survival and overall survival. These first results of the study confirm that DCE-MRI can make an important and non-invasive contribution to the early prediction of therapy response.

In ongoing data analyses, it is investigated to what extent quantitative results gained from diffusion-weighted and DCE-MRI are suitable for assessing the effect of therapy on actual tumor size. Further analyses will evaluate the contribution the method can make to aiding decisions on therapeutic management in routine clinical practice, such as dosage fine-tuning and handling of serious complications.

Further Information

Rheinheimer S, Christopoulos P, Erdmann S, Saupe J, Golpon H, Vogel-Claussen J, Dinkel J, Thomas M, Heussel CP, Kauczor HU, Heussel G (2022). Dynamic contrast enhanced MRI of pulmonary adenocarcinomas for early risk stratification: higher contrast uptake associated with response and better prognosis. *BMC Med Imaging* 22(1):215.

DZL Clinical Trial Board
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

Titel der Studie	Leitende Wissenschaftler	Krankheitsbereich	Participating DZL Partner Sites
EMO-Lung: Monitoring of patients with NLCLC – epigenetic analysis of liquid biopsies and RNA-analysis in exhaled breath condensates	Reck M / Ammerpohl O	Lung Cancer	ARCN, BREATH, CPC-M, TLRC, UGMLC
Right Heart 3: Influence of specific PAH medication on right ventricular function in patients with pulmonary arterial hypertension	Seeger W / Ghofrani A	Pulmonary Hypertension	BREATH, 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	Vogel-Claussen J	Pulmonary Hypertension/ Platform Imaging	BREATH, CPC-M, TLRC, UGMLC
ANAKIN: A phase IIa trial to evaluate safety and efficacy of subcutaneous administration of anakinra in patients with cycstic fibrosis	Sommerburg O	Cystic Fibrosis	ARCN, BIH, TLRC, UGMLC
Neomun Trial: Neoadjuvant anti-PD-1-immunotherapy in resectable NSCLC	Eichhorn M / Savai R	Lung Cancer	TLRC, UGMLC
Eradicate: Inhaled Levofloxacin in adult bronchiectasis patients with early asymptomatic Pseudomonas aeruginosa infection	Behr J / Mertsch P / Ringshausen F / Rademacher J	Bronchiectasis Disease	BREATH, CPC-M, UGMLC
CatBOS: Cathepsin-B (CatB) as a new biomarker and therapeutic target for early bronchiolotis obliterans syndrome (BOS) after lung transplantation	Kneidinger N / Yildirim AO / Hecker M	End-Stage Lung Disease	CPC-M, UGMLC
HANSE study: Holistic Implementation study assessing a Northern German interdisciplinary lung cancer screening effort	Vogel-Claussen J / Bohnet S / Reck M	Lung Cancer	ARCN, BREATH
LeT-COPD: Lymphotoxin-Expressing T-Cell Subtype Facilitates Tissue Injury in COPD Pathogenesis	Yildirim A / Kahnert K / Watz H / Trinkmann F	COPD	ARCN, CPC-M, TLRC
Anti-TSLP-mab: Tezepelumab (Anti-TSLP monoclonal antibody) in progressive interstitial lung fibrosis with evidence of eosinophilia	Prasse A / Seeliger B	DPLD	ARCN, BREATH, CPC-M, TLRC
INSURG-IPF: Proof-of-Principle Study on Inhaled Lung Surfactant in Patients with Idiopathic Pulmonary Fibrosis	Günther A	DPLD	CPC-M, UGMLC
TDM CFTR: Therapeutic Drug Monitoring (TDM) of CFTR Modulators for Improving Pharmacokinetic Modeling and Bayesian Dose Adjustment.	Behr J / Nährig S	Cystic Fibrosis	CPC-M, TLRC

DZL Collaborations, Partnerships, and Networks

At the DZL, over 270 scientists and their research groups from a total of 29 university and non-university research institutions as well as clinics collaborated in the year 2022 across five DZL sites in Germany and additional sites of associated partners. Therefore, intensive exchange among DZL researchers across locations and the entire consortium with external partners is of great importance to dedicate themselves to the common goal of combating lung diseases. In addition to weekly telephone conferences and numerous regular meetings of working groups, committees, and administrative units, the **annual meeting** is noteworthy for this purpose. After a one-year hiatus due to the COVID-19 pandemic, it was able to take place again in 2022 (see p. 38).

Since its establishment, the DZL has been involved in several networks to investigate various lung diseases and is associated with other organizations contributing to the realization of research projects. The expansion and development of **partnerships in the areas of science and research, career development, patient information and advocacy, clinical trials, industry, and public awareness** are actively pursued. Numerous **collaborations at national and international levels** strengthen the position of the DZL as an outstanding institution and the largest German research network in the field of lung research.

The DZL closely collaborates with the **Lung Information Service (LIS)** based at the Helmholtz Zentrum München, supporting the provision of easily understandable information on research and clinical aspects of lung diseases. Together, the DZL and the LIS focus on the interests of patients. More details about their joint activities can be found in the “The Public Face of the DZL” chapter on p. 38 of this annual report.

The cooperation with **COSYCONET (German COPD and SYstemic consequences – COmorbidities NETwork)** has been in place since the establishment of the DZL. This nationwide register for the COPD lung disease involves 29 study centers and conducts a long-term observation of over 2,800 COPD patients as part of the COSYCONET cohort study. The goal is to provide new data on the development, severity, and comorbidities of the disease. COSYCONET, integrated as an associated partner since 2016, contributes to the DZL’s efforts.

The **German Competence Network for Community Acquired Pneumonia (CAPNETZ)** has been an associated partner since early 2013. The competence network aims to gain new insights into the development and course of community-acquired pneumonia (CAP), improve diagnostic standards and therapies, and strengthen awareness and prevention. Pneumonia is annually responsible for up to 20,000 deaths in Germany alone, making it a potentially life-threatening condition. With the largest epidemiological study in Europe, encompassing over 12,000 patients with CAP, and the world’s most extensive database on community-acquired pneumonia, the DZL has gained a strong partner in this field. Additionally, the DZL has expanded its network with scientists and study centers across Europe. For example, CAPNETZ is involved in **PREPARE (Platform foR European Preparedness Against (Re)emerging Epidemics)**, a program funded by the European Union to research infections with epidemic potential.

Registers and patient cohorts are of great and continually increasing importance for the translational research of the DZL. Large cohorts and registers are introduced into the DZL by associated institutions. For example, the DZL, in collaboration with CAPNETZ, has been actively involved since 2015 in establishing the Bronchiectasis Register **PROGNOSIS (The Prospective German Non-CF-Bronchiectasis Registry)** and the pediatric CAP cohort Ped-CAPNETZ. PROGNOSIS is also part of the EU-funded register **EMBARC (European Multicentre Bronchiectasis Audit and Research Collaboration)** and has been an associated partner of the DZL since the turn of the year 2016/17. Additionally, DZL scientists actively participate in many other registers and cohorts, such as the **Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA)** or the National Health Study (NAKO).

The **National Health Study (NAKO)**, initiated in 2014, is the largest German population study to explore common diseases. Since its inception, the DZL has been connected through its own scientists, participating in the long-term

observation spanning 20 to 30 years. Since 2017, there has been an associated partnership between the DZL and NAKO. In collaboration, projects focusing on the prevalence of lung health and lung diseases, as well as other research endeavors, are pursued.

The long-standing collaboration of the DZL researchers with **PROGRESS (Pneumonia Research Network on Genetic Resistance and Susceptibility for the Evolution of Severe Sepsis)** was formalized with the turn of the year 2016/17 through the inclusion of the network as an associated partner. The research focuses on investigating the genetic foundations for the development of the disease and resistance to community-acquired pneumonia. The central question in the research is which factors influence whether pneumonia takes a straightforward course or a severe one, potentially leading to septic shock.

Since 2015, there has been an associated partnership with the **Pulmonary Research Institute (PRI)** located at the LungenClinic Grosshansdorf. The PRI possesses a comprehensive range of methods for examining functional changes and inflammatory processes in the lung. Cohort projects in the field of chronic obstructive pulmonary disease (COPD) and bronchial asthma are conducted, as well as clinical studies in phases I-IV in the field of pneumology, with a focus on COPD, bronchial asthma, and rarer diseases. This new partnership has further intensified the already longstanding close collaboration with LungenClinic Grosshansdorf and the DZL.

The **Robert Koch Institute (RKI)** is the central institution of the German government in the field of application- and action-oriented biomedical research. It possesses a unique population-based database for non-communicable and communicable lung diseases. An associated partnership with the RKI was established in March 2017. This partnership significantly strengthened the DZL's expertise in the crucial field of epidemiology. The utilization of RKI-relevant data particularly contributes to DZL research in areas such as asthma, allergies, COPD, pneumonia, acute lung damage, and lung cancer. Additionally, collaboration exists in various pilot projects related to infections.

In addition, an associated partnership with the **Berlin Institute of Health (BIH)** was initiated in 2017 and formally agreed upon in March 2018. This collaboration includes, among other things, joint projects in translational lung research focusing on cystic fibrosis. Further collaborations exist in the disease areas of Pulmonary Hypertension, Pneumonia & Acute Lung Failure, as well as Asthma & Allergy.

Also, at the beginning of 2020, the DZL was further strengthened by the establishment of the **Institute for Lung Health (ILH)** in Giessen. The joint funding from the Federal Ministry of Education and Research (BMBF) and the Hessian Ministry of Science and the Arts (HMWK), under the umbrella of the DZL, provides valuable growth by establishing five new chairs and additional working groups focusing on vascular and parenchymal (pathological) changes and their repair/regeneration. A dedicated research building, funded by the State of Hesse, is currently in the preparation phase.

Since the inception of the DZL, the **German Respiratory Society (Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin e. V. - DGP)** has been a crucial strategic partner of the center. Collaborations, especially in the promotion of young lung scientists and physicians, as well as in the exchange with patient organizations, are continuously strengthened. The DZL is regularly represented at the annual congresses of the DGP (see p. 38 and following). Members of the DZL's board and scientists have held and continue to hold key positions within the DGP, contributing significantly to the advancement of joint activities. For instance, DZL board member Prof. Dr. Klaus F. Rabe (Grosshansdorf/Kiel) served as the DGP president until March 2019. Currently, Prof. Dr. med. Hortense Slevogt and Prof. Dr. med. Antje Prasse (both from Hannover) represent the DZL in the DGP board.

The **Society for Pediatric Pneumology (Gesellschaft für pädiatrische Pneumologie e. V. - GPP)** promotes research, networking, and the exchange of knowledge among scientists and clinicians, particularly in the field of pediatric pulmonology. As such, the GPP is a significant partner in pediatric pneumology. The GPP regularly organizes scientific symposia and workshops, incorporating research content from the DZL. Researchers from the DZL hold key positions within the GPP, actively participating in the scientific working groups of the professional society. Several DZL researchers are also represented in the GPP's

board, ensuring a robust 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 medical collaborative research in Germany. The DZL collaborates closely with the TMF, particularly in the areas of biobanking and the establishment of a Central Data Management system. There is a regular and intensive exchange of information, especially in the field of biobanking, involving responsible individuals from the German Centers for Health Research and the German Biobank Node (GBN).

The DZL also actively supports various **anti-smoking campaigns**. One of these campaigns is the **Education against Tobacco (AGT)**, initiated in 2012. Each year, over 1,500 medical students from more than 30 faculties in Germany, Austria, and Switzerland volunteer to effectively educate over 20,000 seventh-grade students about the dangers of tobacco smoking. They work towards creating smoke-free classes in schools. Besides students, the project involves lecturers, doctors, and professors. The Chairman of the DZL Executive Board and other DZL researchers are members of the Scientific Advisory Board of this initiative. The initiative received recognition, with the former German Chancellor awarding it the **Federal Prize as part of the „startsocial" competition** for outstanding volunteer projects in Germany in 2014 and 2017. In 2018, it was further honored with the **EU Health Award** by the European Commission.

The DZL collaborates with other **German Centers for Health Research (DZG)** to facilitate nationwide networking in medical-translational research. This collaboration involves regular exchanges on common strategic, infrastructural, and scientific themes at various levels of work. Through this collaboration, synergies can be better utilized and established for the benefit of patients. Areas such as lung cancer, COPD, pneumonia, and pulmonary hypertension, which overlap in the field of lung research, are addressed through joint activities and focus areas detailed in the annual report (see p. 41).

The **European Respiratory Society (ERS)** is a crucial partner for the DZL in the field of respiratory medicine, being one of the largest and most significant societies in this field. The collaboration is evident in various ways, such as the appointment of Professor Dr. Tobias Welte as the President of ERS for the term 2018/19. Additionally, DZL scientists played a key role in organizing the ERS International Congress 2014 in Munich, including holding the position of Congress President. The DZL consistently participates in the ERS annual congress, with an information stand and presentations by DZL scientists. The ERS Congress is recognized as the largest gathering of respiratory researchers and clinicians globally.

Doctors at the DZL are actively involved in ensuring optimal diagnosis and treatment for lung diseases. Their commitment includes contributing to keeping **treatment guidelines** up to date. Medical guidelines play a crucial role in supporting physicians in the treatment of their patients by reflecting the current state of well-established research findings. They serve as a vital interface between scientific knowledge and medical practice.

Beyond these, there are numerous other strategic partnerships between individual DZL locations and international partners from the fields of science and business. **Prof. Maria Belvisi**, through her role as a member of the International Scientific Advisory Board, contributes to enhancing the DZL's expertise in industrial contacts. DZL scientists are currently collaborating with over 100 international partners from the business sector, particularly in fundamental and applied research projects, as well as in conducting clinical studies. These clinical studies, especially those oriented towards approval, are operated 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: Supporting Early Career Scientists

The DZL offers attractive research positions for excellent national and international early career scientists. A vibrant early career scientist community is a key asset for meeting the current and future challenges presented by respiratory medicine and creates a strong foundation for innovation in lung research. We support the career development of students, doctoral candidates, and post-doctoral researchers in medicine and the life sciences related to clinical, translational, and basic lung research. The Academy organizes scientific symposia and funds mobility grants for research exchange between DZL sites. We are also committed to ensuring that early career scientists benefit from the family-friendly programs and infrastructures at the various DZL sites. In addition to offering a wide range of site-specific graduate programs and other career-development opportunities (please refer to the DZL Academy website for a complete listing: www.dzl.de/en/the-dzl-academy), the DZL Academy aims to strengthen the early career scientist's sense of belonging to the DZL community. A supportive environment serves to build a strong peer network within and beyond the DZL.

DZL Academy Board

The DZL Academy Board is composed of researchers, clinician scientists and project managers from all five DZL sites as well as the five elected representatives of the DZL Academy Fellow Community. It is dedicated to the conceptual and strategic planning of the promotion of early career scientists.

Goals Achieved in 2022

- ✅ Continuation of the digital lecture program
- ✅ Organization of the DZL Academy Symposium 2022
- ✅ Organization of workshops for DZL Academy Fellows
- ✅ Organization of courses as part of the Mentoring Program
- ✅ Coordination of activities of the DZG Working Group Early Career Scientist Development 2022
- ✅ Mobility Grants in support of training and scientific exchange between DZL sites

Goals 2023

- Continuation of the digital lecture program
- Continuation of the Mentoring Program
- Organization of the DZL Academy Symposium 2023 & Workshops
- Mobility Grants in support of training and scientific exchange between DZL sites
- DZL Academy Publication Award
- Joint organization of the DZG Science and Career Day 2023

DZL Academy Symposium 2022 - Early career lung scientists meet at Rauischholzhausen

On 21-23 November 2022, the DZL Academy hosted its Annual Symposium titled “Lung Development, Repair and Regeneration”. In the suitably remote and beautiful grounds of Rauischholzhausen, Hessen, about 50 early career scientists mingled and exchanged ideas on hot topics in lung research and career paths with an international group of leading scientists in the field.

In his opening address, keynote speaker Dr. William Zaccharias (Cincinnati Children’s Hospital Medical Center, Cincinnati, USA) set the scene, highlighting the fact that despite global research efforts, we still have no therapies available to patients to promote the regeneration of diseased lungs. The keynote address by Dr. Purushothama Rao Tata (Duke University, Durham, USA) and Dr. Kerstin Meyer (Wellcome Sanger Institute, Cambridge, UK) honed in on the great advances that have been made in our understanding of lung development and regeneration with the application of single-cell technologies. In her concluding keynote address, Dr. Darcy Wagner (Lund University, Sweden), pushed the frontiers of medical approaches to promote lung regeneration further by outlining her work with 3D printing of lung tissue structure.

A special excursion to another very topical respiratory system was presented the Dr. Hartmut Michel (Max Planck Institute of Biophysics, Frankfurt), recipient of the 1988 Nobel Prize in Chemistry, who summarized the milestones met along the path of studies on of photosynthesis and cellular respiration.

The symposium was organized by the DZL Academy board members Professor Rory E. Morty (TLRC) and Professor Elie El Agha (UGMLC) with the support of Dr. Sezin Czarnecki (UGMLC).

The aim of the event was to gather early career and established scientists from basic research and clinical practice, to stimulate interdisciplinary discussions and to advance translational lung research and highlight career development strategies. In this sense, the symposium was a great success, as Professor Rory E. Morty summarized at the end of the symposium: “To be able to drive regeneration of the diseased lung, by understanding and exploiting developmental and regenerative pathways, represents the only hope we currently have for the long-term management of a number of acute and chronic lung diseases for which curative therapies do not exist. Our DZL Academy Annual Symposium succeeded in bringing trainee scientists drawn from all DZL sites who work in this exciting and challenging arena together with the leading minds in the field to help their research move forward”.

DZL-Academy Symposium 2022

DZG Early Career Scientist Symposium on Cutting-Edge Single Cell Analyses

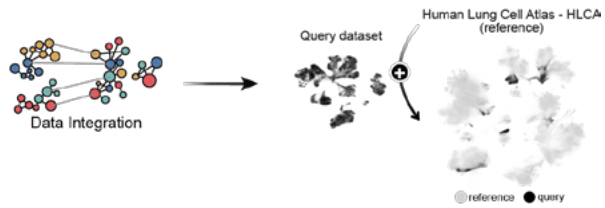
The six German Centers for Health Research (DZG) jointly organized a first symposium for early career scientists to discuss the cutting-edge developments and techniques of single cell analysis in research and medicine. 120 early career scientists working in clinical and basic research discussed with experts about single cell technologies and their application during the online event on 10-11th November 2022.

Single-cell analyses are currently revolutionizing basic science and promise numerous new approaches for the development of novel therapeutic approaches to combat widespread common diseases, which are at the heart of the research conducted by the DZG. A plethora of methods employed in single cell analyses allows researchers to generate highly precise data about cell types and developmental states of single cells in healthy and diseased tissues. The interpretation of these data (single-cell omics) generates new insights and understanding of complex biological changes within an individual cell, for instance due to aging processes, adaptation to environmental conditions or as a consequence of diseases. There are multiple technologies for single-cell analyses and more than 1,400 software applications for data analyses.

How to choose the right tool?

The early career scientists discussed about choosing the appropriate tool and many other questions with Prof. Joachim Schultze, expert for swarm learning and artificial intelligence, and Prof. Fabian Theis, expert for modelling cell metabolism by single-cell sequencing.

It was the aim of this symposium to bring together experts and early career scientists from all DZG, working in clinical and/or basic research, to facilitate interdisciplinary discussions about single-cell analysis applications and to learn from each other. In this context the symposium was a success as Dr. Herbert Schiller (scientific coordinator of the event, Helmholtz Munich) summarized after the event: “Cells are the fundamental units of life. Hence, it is essential to look at the single cell for insights into complex biological processes in our bodies and to identify pathological changes that will result in disease. In recent years, single-cell analysis has allowed scientists to establish a kind of `google maps´ of the human body (Human Cell Atlas). In my view, the event succeeded in training early career scientists by bringing together experts that provided excellent examples for applied research in this dynamic field of single-cell genomics.”



The establishment of the Human Cell Atlas (HCA) enables fast interpretation of newly generated data based on different lung diseases and thus offers new possibilities for translational research in the German Center of Lung Research.

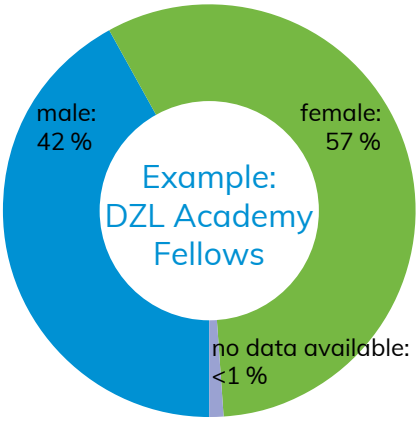
Equal Opportunities and Diversity

The German Center for Lung Research (DZL) and its member institutions are committed to promoting equal opportunities and gender equality at the respective DZL sites. For the DZL and its member institutions, it is understood that no one should be excluded from a scientific career based on gender, ethnic origin, nationality, age, or health status. Equal opportunities and gender equality yield multiple benefits, as they allow for the full utilization of existing innovation and talent potential and enhance the quality of research through diverse and inclusive workgroups.

In close collaboration with the relevant committees at the respective DZL sites, talents are actively sought to make the DZL more diverse, innovative, and creative. Concrete measures, such as gender equality and equal opportunity programs, are implemented by our member institutions. Within these programs, efforts are made at every level, from trainees to the Scientific Advisory Board, to specifically recruit female researchers and increase the proportion of female staff. The goal is to particularly expand the number of female DZL employees in leadership positions. Since the establishment of the DZL in 2011, the percentage of female Principal Investigators (PIs) has increased from 14% to approximately 28% (as of 2023). In 2022, the percentage of female employees in the overall personnel is 71%. Read more about personnel and gender equality on p. 55.

Nationalities of the 464 DZL Academy Fellows

Equal Opportunities and Diversity



The Public Face of the DZL

Respiratory diseases are among the most common causes of death in Germany. However, they remain significantly underrepresented in the public perception of prevalent public health issues. Therefore, at the DZL, we consider it a crucial mission to educate the general public, decision-makers, patients, and their families about respiratory diseases and lung health.

Comprehensive information is available to interested individuals on the website www.dzl.de. The website showcases the ten disease areas and platforms investigated at the DZL, featuring all our scientists. It also provides insights into our efforts in promoting young talent and other background information about our research. In the news section, we regularly share current research findings, and past annual reports are available for download in both German and English. Since 2022, we have been sending out our newsletter “DZL Inside” twice a year.

Our digital information offering is complemented by our presence on social media platforms such as Twitter, LinkedIn, and Instagram, as well as our promotional film on YouTube. We also contribute regular posts on the joint channels of the German Centers for Health Research (DZG), sharing insights from lung research. Since 2019, the DZG have been publishing the collaborative magazine “SYNERGIE – Forschen für Gesundheit” twice a year, available in both print and online versions (refer to p. 41 for more information on DZG collaborations).

In May 2022, the DZL made a significant impact at the 62nd Congress of the German Respiratory Society (DGP) in Leipzig, with an information booth, numerous award winners, and presentations by scientists from our ranks. The DGP Congress is the largest scientific forum in the field of pneumology in the German-speaking region.

The DZL Annual Meeting remains the largest and most significant gathering of our researchers. After a one-year hiatus , the 10th meeting took place in Hannover in 2022. On July 6th and 7th, well over 500 researchers from across Germany convened at the Hannover Congress Center to exchange insights, developments, and challenges in the field of lung research, marking the 10th anniversary of the DZL.

Focus on Patients

In its strategic orientation, the DZL increasingly focuses on the concerns and interests of patients. The Lung Information Service (LIS) has been a professional and reliable partner for the direct and easily understandable information for patients since the establishment of the DZL. The LIS provides scientifically sound, current, and unbiased information directly from research to improve people's health and health literacy. In 2022, an average of 160,000 people per month accessed the LIS website. The access numbers have thus stabilized at approximately ten percent above the 2020 level after a peak related to the pandemic.

The LIS conveys information through a comprehensive online portal, patient events, Twitter, and publications. The LIS provides foundational knowledge and new research findings in an understandable manner at www.lungeninformationsdienst.de. In mid-November 2022, the portal underwent a relaunch with a new design and improved functionality, particularly for users of mobile devices. Key topics on the online portal of the Lung Information Service in 2022 included asthma, lung transplantation, COPD, clinical studies, and bronchopulmonary dysplasia. The demand for reliable health information on current topics was evident in 2022, particularly regarding the respiratory syncytial virus (RSV). Similar to the previous year, the wave of respiratory infections and RSV infections was unusually high in 2022.

The scientists and physicians at the DZL sites serve in an advisory capacity for the editorial contributions of the LIS and individual patient inquiries to the LIS. Typically, DZL and LIS organize several forums each year specifically for patients and their families, each with over 100 participants. Since 2016, DZL and LIS have also provided an overview of current clinical studies conducted by DZL scientists for patients, families, and the general public. In the online directory on the LIS websites, goals, inclusion criteria, duration, and examination or treatment methods of each study are presented in an understandable way. Interested patients can directly contact the study centers through the platform, facilitating easier access to clinical trials. The directory is regularly updated, and by the end of 2022, around 160 different studies categorized by disease will be covered.

In 2022, the LIS published four articles in the magazine "Patient Library - Airways and Lungs" (circulation 30,000) in its dedicated section "Current Lung Research" (Lung Research Update). In these articles, scientists, including Prof. Dr. Werner Seeger (UGMLC) and Prof. Dr. Peter Alter (UGMLC), provided statements on the work of the German Centers for Health Research and COSYCONET. Additionally, Dr. Gizem Güneş Günsel (CPC-M) and Niklas Lang (CPC-M) shared insights into their research, for which they received recognition at the Annual Congress of the German Society for Pulmonology and Respiratory Medicine.

As of the end of 2022, the monthly newsletter of the LIS reached over 4,100 subscribers. On Twitter, LIS publishes updates from research approximately five times per week, garnering more than 800 followers by the end of 2022.

An essential contribution to enhancing the representation of patient interests in the DZL is made by Dr. Pippa Powell, Manager of the European Lung Foundation (ELF), through her membership in the Scientific Advisory Board of the DZL. Since the founding of the European Respiratory Society (ERS), the ELF has aimed to bring together patients, the public, and professionals in the field to make a positive contribution to pneumology. One notable success arising from this collaboration is the publication of the German translation of the European Patient Ambassador Programme (EPAP). This free online program is designed for patients, caregivers, and nursing staff. Through the course, participants can enhance their skills in information retrieval and communication with medical professionals, policymakers, researchers, and the media. The program is suitable for patients with various illnesses, developed by

ELF and is now available in German, in addition to English, French, Italian, and Dutch.

With the Working Group on Patient Involvement, the German Centers for Health Research (DZG) have collectively taken another important step. Health data is a valuable resource for the digital medicine of the future. To efficiently utilize this treasure for the benefit of patients, data must be exchanged, harmonized, and interconnected across institutional and disciplinary boundaries through secure infrastructures. Data protection and security are of paramount importance in this process. Therefore, the values, interests, and needs of patients should significantly reflect in data-driven medical research. For this reason, six patient representatives, alongside twelve scientists from the DZG, actively participate in the Working Group on Patient Involvement.

The German Centers for Health Research (DZG)

The German Centers for Health Research (DZG) are long-term, equal partnerships between non-university research institutions such as Max Planck, Helmholtz, and Leibniz Institutes, and universities with university hospitals. The DZL is one of the six centers established between 2009 and 2012 on the initiative of the Federal Ministry of Education and Research (BMBF). In 2022, DKTK, DZL, DZIF, and DZHK celebrated their tenth anniversary with a joint ceremony in Berlin.

The DZG address the following diseases: Cancer (DKTK), Diabetes (DZD), Cardiovascular Diseases (DZHK), Infectious Diseases (DZIF), Lung Diseases (DZL), and Neurodegenerative Diseases (DZNE). Two more centers will be established in the next two years: The German Center for Mental Health (DZPG) is scheduled to begin its operations in May 2023, while the German Center for Child and Adolescent Health is expected to commence in late 2023.

These centers pool existing expertise, ensuring that new scientific insights into prevention, diagnosis, and therapies for prevalent conditions benefit patients more rapidly. Basic research and clinical research are closely interconnected. The strategic collaboration among leading researchers in the DZG strengthens Germany's position in international competition and enhances its attractiveness for scientific talent both domestically and abroad. The consolidation of various disciplines and competencies has already led to significantly increased international visibility of translational, clinically applied research in Germany.

The six DZG have worked closely from the beginning to exchange experiences and create synergies. Quarterly joint meetings of the DZG boards and semi-annual DZG forums, involving the BMBF and state representations, focus on the strategic development and collaboration of the DZG. In recent years, a DZG office has been established, while existing working groups on Global Health, Promotion of Young Scientists, Public Relations, Patient Participation, and Regulatory Aspects of Clinical Trials continued their work. The Data Management working group was further developed in 2022 and renamed the Research IT working group. It is dedicated to harmonizing processes and IT systems for efficient and secure data exchange between the various specialized centers.

The DZG Innovation Fund (DZGIF) was developed as a joint research funding program. It commenced in 2022 with its first call for proposals on the research theme "Gene and Cell Therapy". The fund aims to enhance the collaboration among DZG members within the German research landscape and foster interdisciplinary synergies. Researchers from five of the six DZG are involved in the successful application. In a second call for proposals on the theme "Microbiome", eight full applications were submitted by the deadline at the end of November 2022.

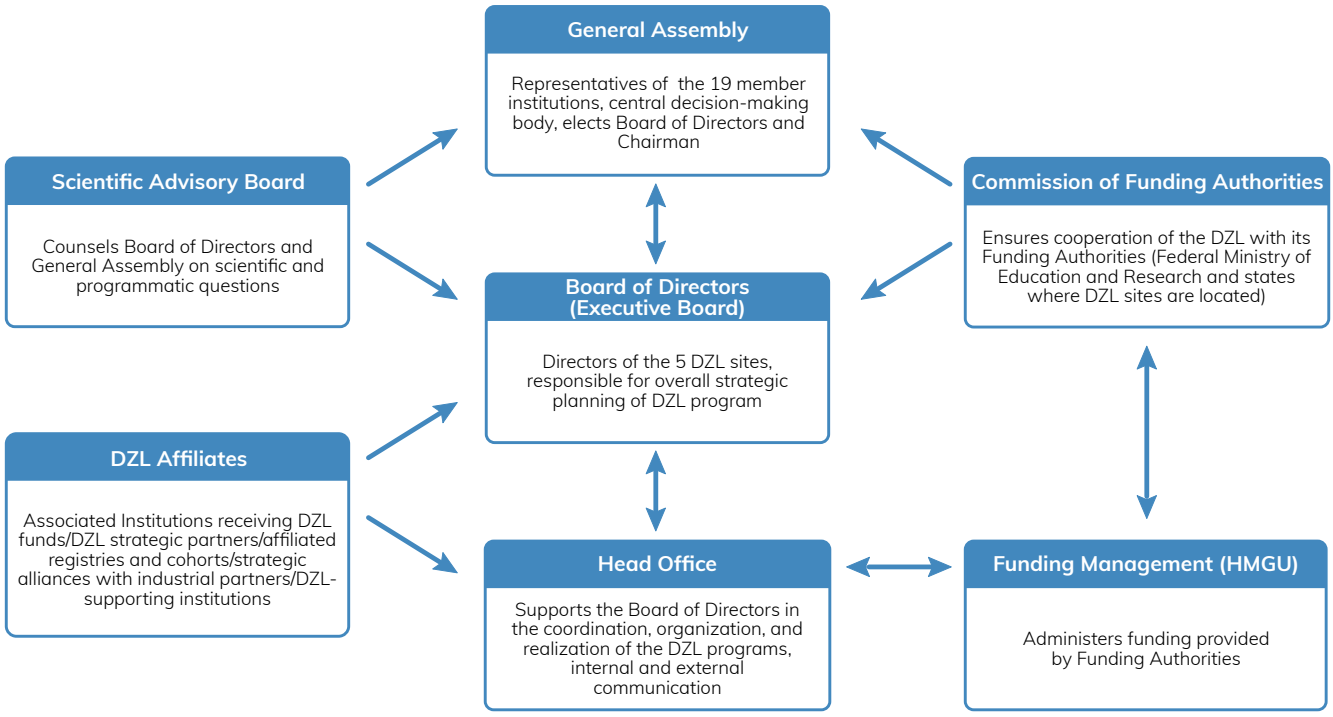
In the realm of promoting young scientists, the DZG offered courses for young talents last year, such as the DZG Symposium for young researchers on "Single-Cell Analysis" and several lectures on science communication, career development, and business founding. Additionally, efforts were made to support scientists in balancing clinical work and research and exchanging their research data and bio samples based on common standards.

With a jointly organized symposium followed by a public citizens' event featuring a panel discussion on the topic of Post-COVID Syndrome, the DZG also contributed to the scientific discussion on the long-term effects of COVID and their implications for healthcare in Germany in 2022.

The jointly conceived health research magazine SYNERGIE continued in 2022 with two issues on "The Immune System" and "Clinical Research"—available both in print and online at www.dzg-magazin.de. In 2022, it received an iF DESIGN AWARD in the Communication category, marking the second design award for the magazine following the Silver Berliner Type award in 2021.

DZL Annual Meeting 2022 in Hanover

DZL Organization



ARCN	BREATH	CPC-M	TLRC	UGMLC	
4 member institutions + 3 associated partners	3 member institutions + 1 associated partner	4 member institutions	5 member institutions	3 member institutions	6 further associated partners, nationally organized or based outside the DZL sites

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, Lubeck (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)

Geschäftsstelle

- Dr. Christian Kalberlah, Managing Director
- Susanne Klasen, Management Assistant
- Christin Krakau, Management Assistant
- Natalie Liebel, Management Assistant
- Rogin Honar, 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. In 2022 the twelve members of the Scientific Advisory Board were:

Dr. Jacob I. Sznajder (MD)
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

Prof. Dr. Peter M. Suter
Vice Chairman of the Scientific Advisory Board
Akademien der Wissenschaften Schweiz, Centre Médical Universitaire, Universität Genf; SUI

Prof. Dr. Peter J. Barnes
Head of Respiratory Medicine, Imperial College London; UK

Prof. Maria Belvisi
Senior Vice President and Head of Research and Early Development, Respiratory & Immunology, BioPharmaceuticals R&D, AstraZeneca; SWE; Professor of Respiratory Pharmacology, NHLI, Imperial College London; UK

Prof. Dr. Rachel Chambers
Professor of Respiratory Cell and Molecular Biology, Center for Respiratory Research, University College London; UK

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

Prof. Dr. 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; IRL

Prof. Dr. med. Urs Frey
Medical Director, Chief Physician Pediatrics, Member of the Executive Board, University Children's Hospital Basel; SUI

Prof. Dr. Mark Gladwin
Division Chief, Pulmonary, Allergy and Critical Care Medicine, Director Vascular Medicine Institute, University of Pittsburgh Medical Center; USA

Dr. Pippa Powell
Director of the European Lung Foundation (ELF), Sheffield; UK

Prof. Dr. Hans-Ulrich Prokosch
Holder of the Chair for Medical Informatics, Friedrich-Alexander-Universität Erlangen-Nürnberg; Chief Information Officer, Universitätsklinikum Erlangen; Former Member of the Board of the German Society for Medical Informatics, Biometry and Epidemiology (GMDS); GER

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

Head of Funding Management

Dr. Florian Mertes – Finanzabteilung (Kaufmännisches Fördermittelmanagement, Helmholtz Zentrum München)

General Assembly

The DZL currently has 19 member institutions. In addition, the DZL has ten associated partners (as of 2022).

Commission of the Funding Authorities

- Federal Ministry of Education and Research (Chair)
- Baden-Württemberg – Ministry of Science, Research and Arts
- Bavaria – Bavarian State Ministry for Science and the Arts
- Hesse – Hessian Ministry of Higher Education, Research, Science and the Arts
- Lower Saxony – Lower Saxony Ministry for Science and Culture
- Schleswig-Holstein – Ministry of General Education and Vocational Training, Science, Research and Culture

DZL Member Institutions and Sites

Kiel/Lübeck/Borstel/Grosshansdorf

Airway Research Center North (ARCN)

Site Director: Prof. Dr. Klaus F. Rabe

- Kiel University
- Research Center Borstel – Leibniz Lung Center
- LungenClinic Grosshansdorf
- University of Lübeck

Hanover

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

Site Director: Prof. Dr. Tobias Welte

- Fraunhofer Institute for Toxicology and Experimental Medicine, Hanover
- Leibniz University Hannover
- Hannover Medical School

Giessen/Marburg/Bad Nauheim

Universities of Giessen and Marburg Lung Center (UGMLC)

Site Director: Prof. Dr. Werner Seeger, also DZL Chairman, and Speaker

- Justus-Liebig-Universität Giessen
- Max Planck Institute for Heart and Lung Research, Bad Nauheim
- Philipps-University Marburg

Heidelberg

Translational Lung Research Center Heidelberg (TLRC)

Site Director: Prof. Dr. Hans-Ulrich Kauczor

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

Munich

Comprehensive Pneumology Center Munich (CPC-M)

Site Director: Prof. Dr. Dr. h. c. Erika von Mutius

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

Associated Partners of the DZL

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


Kiel
Lübeck
Borstel
Grosshansdorf
Hanover
Marburg
Giessen
Bad Nauheim
Heidelberg
Munich

DZL Site Borstel, Lübeck, 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 Hospital Schleswig-Holstein – Kiel Campus
- Kiel University
- LungenClinic Grosshansdorf
- Pulmonary Research Institute at the LungenClinic Grosshansdorf

Prof. Dr. Dr. h.c. Klaus F. Rabe

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

Contact
DZL Site Coordinator, ARCN:
Dr. Jörn Bullwinkel
E-Mail: j.bullwinkel@lungenclinic.de
Phone: +49 4102 601-2410

Research Profile
Chronic Obstructive Pulmonary Disease (COPD), Lung Cancer (LC), and Asthma & Allergy (AA) constitute the research focus at the Airway Research Center North (ARCN). This translational research consortium brings together the expertise of research and medicine in the field of pneumology in Schleswig-Holstein. The LungenClinic Grosshansdorf, as the largest northern German specialized clinic for lung and respiratory diseases, along with the University Medical Center Schleswig-Holstein (UKSH), is responsible for the clinical and patient-related research of ARCN, treating nearly 12,000 patients annually. The Borstel Research Center focuses on the investigation of infectious and non-infectious lung diseases, contributing to the success of ARCN in basic research and the development of animal models. Other partners include researchers from the University of Lübeck and the Christian Albrechts University of Kiel, dedicated to studying asthma in animal models, analyzing epigenetic causes of lung diseases, and developing novel imaging methods. Collaborating with the Pneumological Research Institute at LungenClinic Grosshansdorf, we conduct cohort projects and clinical studies. To strengthen the connection between clinic and basic research, the Biomaterialbank Nord has been established as a shared central infrastructure. In the field of asthma, our pediatric, adolescent, and adult medicine physicians work collaboratively to better understand different disease progressions. The cross-networking of complementary partners aims to support the cooperative development of translational research approaches.

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 Hanover DZL site BREATH
- Head of the Department of Respiratory Medicine of Hannover Medical School
- Board Member and Treasurer of the Biomed Alliance
- Chairman of the Board of Trustees of the German Lung Foundation e. V.
- Member of the Internal Advisory Board of the German Center for Infection Research (DZIF) (2011-2019)
- President of the European Respiratory Society 2018/19
- President of the Paul Ehrlich Society (PEG) 2018–2020
- Chairman of the Board of Trustees of the CAPNETZ Foundation
- Member of the evaluation group for clinical studies of the DFG since 2016
- President of the German Respiratory Society 2012-2014

Contact
DZL Site Coordinator, BREATH:
Dr. Annegret Zurawski
E-Mail: zurawski.annegret@mh-hannover.de
Phone: +49 511 532-5192

Research Profile
The focus of BREATH is on the translation of findings from basic research into clinical practice in a broad field of different lung diseases. A central component is the conduct of clinical trials in all phases relevant for approval at Hannover Medical School and the Clinical Research Center, a Core Facility of the MHH. Hannover Medical School is one of the largest lung transplant centers in the world, which is why research in the field of end-stage lung diseases is a focus of the site. This includes research in the field of artificial lungs and stem cell research. In the area of preclinical research, infectious diseases, Pulmonary Hypertension, interstitial lung diseases as well as Asthma and Allergic diseases are among the important research fields at the BREATH site. Basic research in the field of infectiology focuses on the pathobiology of bacterial and viral infections, such as SARS-CoV-2, and chronic remodeling processes in the lung. Further research is aimed at a better understanding of the function of the human innate immune system and the control of inflammatory responses in healthy and diseased individuals. In cooperation with the Fraunhofer Institute for Toxicology and Experimental Medicine, the scientists are conducting research on the pathophysiology of allergic diseases. The Leibniz University Hannover contributes significant expertise to the research network in the field of health care research and health economic aspects as well as in the field of imaging based on laser technology. The national research network CAPNETZ aims to improve patient-centered care for adults and children with community-acquired pneumonia (CAP) and participates in the COSYCONET (Competence Network COPD and Asthma) registry and the PROGNOSIS (bronchiectasis) registry, both of which are associated partners of the DZL

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

Partner Institutions of the Site

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

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

- Director of the DZL Site CPC-M
- Head of the Department of Allergy and Asthma at Dr. von Hauner Children's Hospital of Ludwig-Maximilians-Universität München
- Head of the Department Environmental Health at Helmholtz Zentrum München
- Member of the Editorial Board of the New England Journal of Medicine (since 2006)
- Recipient of the Gottfried Wilhelm Leibniz Prize of the German Research Foundation (DFG)
- Bearer of the Cross of Merit on Ribbon of the Order of Merit of the Federal Republic of Germany
- Fellow of ERS (FERS)
- Director of the Institute of Asthma and Allergy Prevention at Helmholtz-Zentrum München

Contact

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

Research Profile

In the Comprehensive Pneumology Center Munich (CPC-M), Helmholtz Zentrum München – German Research Center for Environmental Health, Ludwig-Maximilians-Universität with its University Hospital, and Asklepios Fachkliniken München-Gauting have joined forces to form one of the world's largest centers for translational research into chronic lung diseases. Helmholtz Zentrum München has renowned expertise in integrating basic and applied medical research. Ludwig-Maximilians-Universität is one of the universities funded by the German Excellence Initiative. Its medical staff is committed to achieving cutting-edge university research and medical care in the field of pulmonary diseases at the highest level. Asklepios Fachkliniken München-Gauting is one of Germany's leading hospitals in the field of lung diseases.

The CPC-M focuses on research into chronic lung diseases. For this purpose, scientists combine state-of-the-art techniques in molecular and cell biology, pharmacology, molecular pathology and clinical medicine to develop new diagnostic tools and therapies for chronic lung diseases. In addition to their research program, CPC-M scientists coordinate the disease areas "Interstitial Lung Disease" and "Asthma and Allergy." As an important link between clinical and basic research, CPC-M operates a research outpatient clinic. Here, clinicians and scientists work closely together to apply research results to therapeutic approaches. Moreover, the Lung Information Service (www.lungeninformationsdienst.de), which prepares and makes available lung-related topics for patients and the general public, is located at the CPC-M.

DZL Site Heidelberg
Translational Lung Research Center Heidelberg (TLRC)

Partner Institutions of the Site
- Heidelberg University Hospital
- Heidelberg University
- Thoraxklinik at Heidelberg University Hospital
- German Cancer Research Center (DKFZ)
- European Molecular Biology Laboratory (EMBL)

Prof. Dr. Hans-Ulrich Kauczor

- Director of the DZL site TLRC DZL site
- Medical Director of the Department of Diagnostic and Interventional Radiology at Heidelberg University Hospital
- Professor for Radiology, Heidelberg University
- President of the international Fleischner Society 2015
- President of the European Society of Thoracic Imaging 2011

Contact
DZL Site Coordinator, TLRC:
Dr. Birgit Teucher
E-Mail: birgit.teucher@med.uni-heidelberg.de
Phone: +49 6221 56-32144

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), Chronic Obstructive Pulmonary Disease (COPD), Diffuse Parenchymal Lung Diseases (DPLD) and Lung Cancer (LC). TLRC scientists also contribute to research in the fields of Asthma & Allergy (AA), Pneumonia & Acute Lung Injury (ALI), and Pulmonary Hypertension (PH). 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. Innovative artificial intelligence methodology applied to imaging data is an important hallmark of our research in the area of early detection of lung diseases and their comorbidities. 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)
- Director of the Institute of Lung Health (ILH) , Giessen
- Fellow of ERS (FERS)

Contact

DZL Site Coordinator, UGMLC:
Dr. Sylvia Weißmann
E-Mail: sylvia.weissmann@ugmlc.de
Phone: +49 641 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 impact of environmental factors on the development of Asthma and Chronic Obstructive Pulmonary Disease (COPD) and on treatment of these lung diseases, 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 the healing and repair process. 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 JLU research portfolio is augmented by the founding of the Institute of Lung Health (ILH) in 2020. Funding by the BMBF and the State of Hesse (from 2021 under the umbrella of the DZL) allows for the establishment of three new professorships and further research groups. A new ILH building is planned, financed by the State of Hesse. The Max Planck Institute in Bad Nauheim focuses on 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 such as the Excellence Cluster Cardio-Pulmonary Institute (CPI). Within the DZL, the DZL Head Office as well as the DZL Biobanking and Data Management Platform are located at the UGMLC.

Selected Prizes and Awards 2022

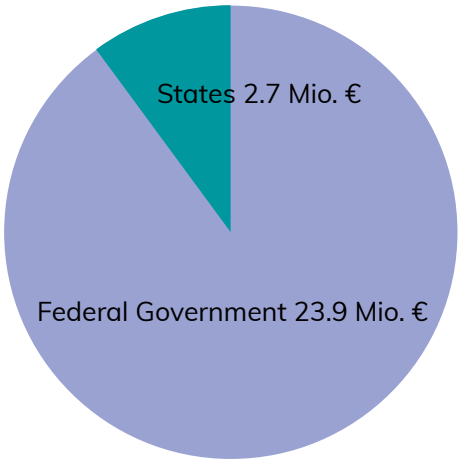
Name and DZL Site	Prize / Award
Prof. Dr. Elie El Agha Giessen	Justus Liebig University Giessen Award
Marija Gredic Giessen	Research Award of the German Respiratory Society (DGP) for the best scientific paper in the field of basic research
Maja Reimann **Dr. Sebastian Marwitz** Borstel **Jan Heyckendorf** Kiel	Research Award of the DGP for the best scientific paper in the field of clinical research
Prakash Chelladurai Giessen	Research Award from the René Baumgart Foundation
PD Dr. Mariel Nöhre Hanover	Research Award from the German Transplant Society 2022
PD Dr. Benjamin Seeliger Hanover	Research Award in Intensive Care Medicine from the German Society for Internal Intensive Care Medicine (DGIIN)
Dr. Srinu Tumpara Hanover	CSL-Behring Alpha1 Science Award 2022
Rachel C. Chambers Wissenschaftlicher Beirat des DZL	Lifetime Achievement Award in Basic and Translational Sciences from the European Respiratory Society (ERS)
Prof. Dr. Marcus Mall Berlin	Global Winner 2022 of the Falling Walls Foundation in the Life Sciences category
Dr. Mark Oliver Wielpütz Heidelberg	Adolf Windorfer Award from the Mukoviszidose e. V., Marie Curie Ring from the German Roentgen Society (DRG), Vertex Innovation Award
DZG-Magazin SYNERGIE	iF Design Award 2022

Finance and Personnel

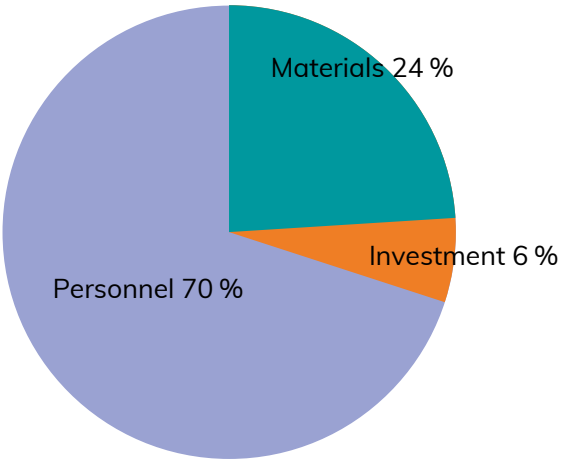
Total Funding and Cost Breakdown 2022

In 2022, the DZL received a total funding of 26.6 million euros. The Federal Ministry of Education and Research (BMBF) contributed 90% of these funds, while the remaining 10% were provided by the federal states where the DZL sites are located. Over 50 major research projects within the eight disease areas investigated by DZL scientists were supported. The DZL Funding Management, situated at the Helmholtz Zentrum München, oversees the financial administration and disburses project funds to the DZL partner institutions. Additionally, the Hessian Ministry of Science and Art directly allocated 2.7 million euros to the Justus-Liebig-University Giessen in 2022 to support the establishment of the Institute for Lung Health (ILH) in Giessen (as of August 2023).

Total Funding 2022



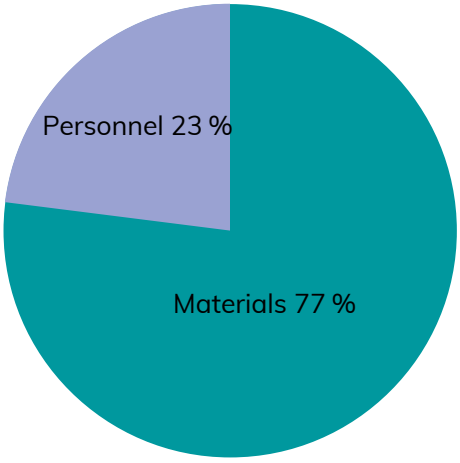
Cost Breakdown: DZL Expenses 2022

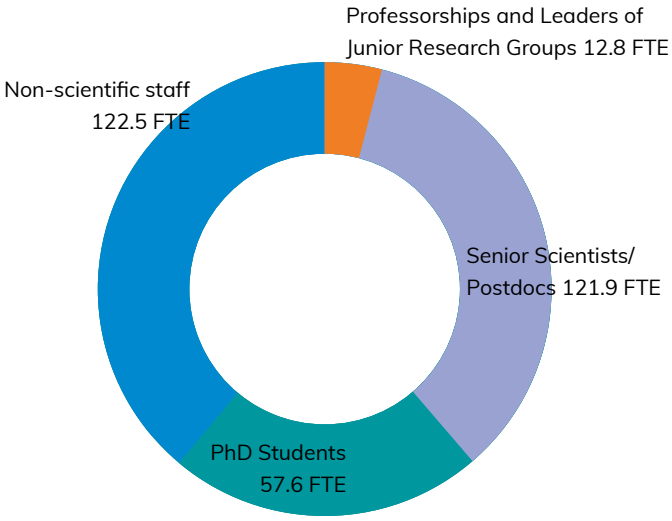


Cost Breakdown: DZL Expenses 2022

The DZL e.V. finances its operations through membership fees from affiliated institutions and donations. In 2022, the association had €654,600 at its disposal from membership fees. The financial statements and the results report for the year 2022 were prepared by the tax and law firm Haas & Haas (Giessen).

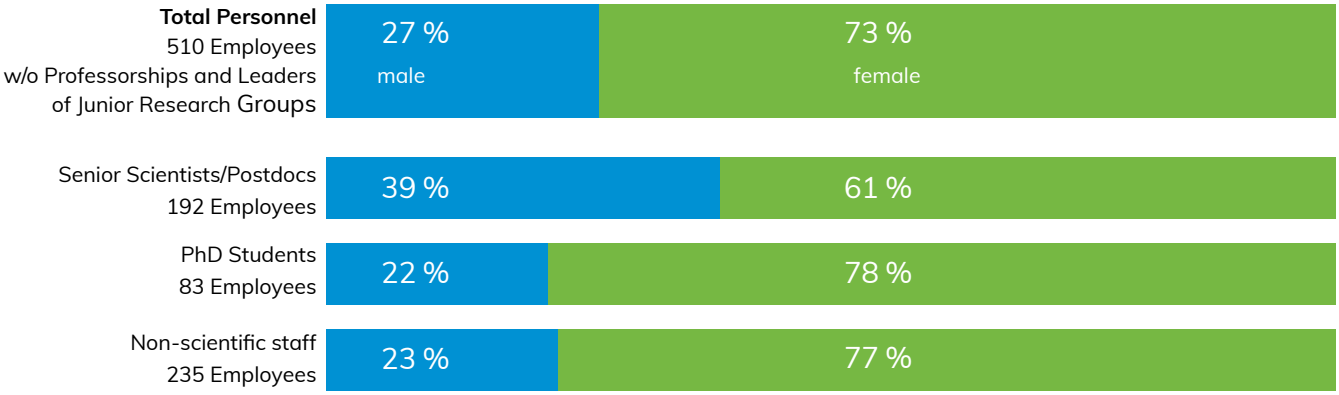
Cost Breakdown: DZL e. V. Expenses 2022





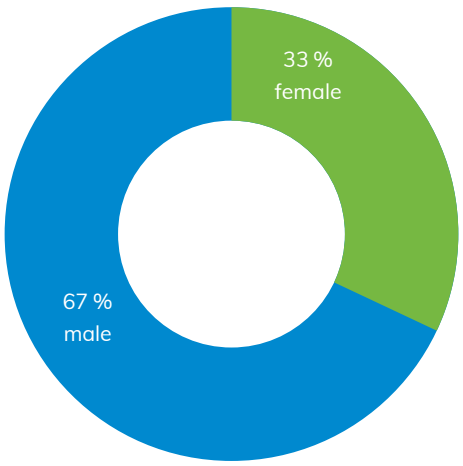
Personnel and Gender Equality 2022

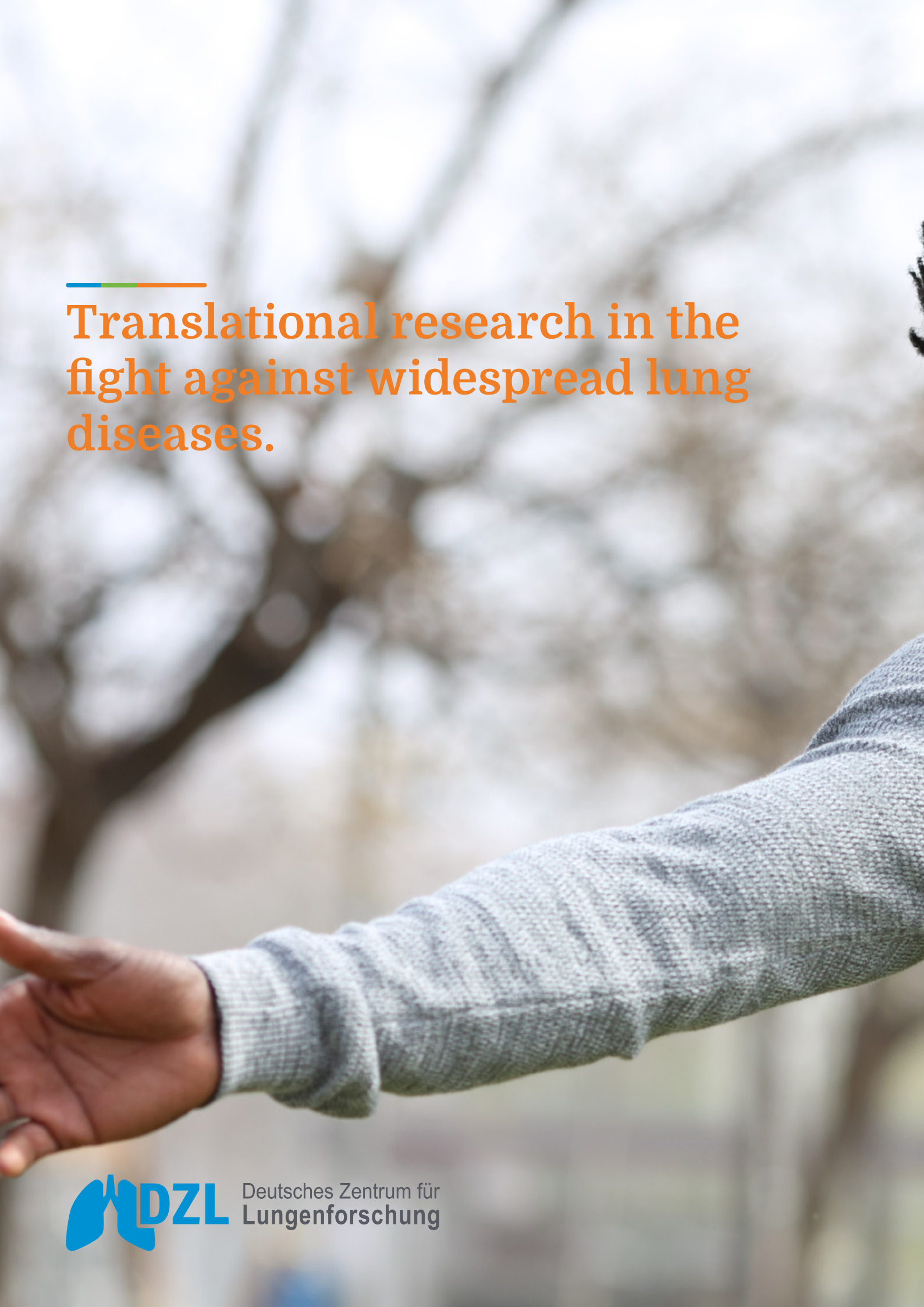
In 2022, employment relationships for 528 individuals (equivalent to 314.7 full-time equivalents, FTE) at the five partner centers and associated partner institutions were funded with DZL money. Of these individuals, 376 were women, accounting for 71% of the total personnel.



Professorships and Leaders of Junior Research Groups 2022

In 2022, 18 professorships and junior group leader positions were funded by DZL resources, with 6 of these positions filled by women, constituting 33%.





Translational research in the fight against widespread lung diseases.

DZL Deutsches Zentrum für Lungenforschung


Funded by
the people of
Germany.

Glossary

AA	Asthma & Allergy
AGT	Education against Tobacco
ALI	Pneumonia & Acute Lung Injury
ALLIANCE	All Age Asthma Cohort
ARCN	Airway Research Center North
ARDS	Acute Respiratory Distress Syndrome
AsCoNet	Kompetenznetz Asthma und COPD
BIH	Berlin Institute of Health
BMBF	German Federal Ministry of Education and Research
BREATH	Biomedical Research in Endstage and Obstructive Lung Disease
CAPNETZ	German Competence Network for Community Acquired Pneumonia
CF	Cystic Fibrosis (Mucoviscidosis)
CFTR	Cystic Fibrosis Transmembrane Conductance Regulator
CLAD	Chronic Lung Allograft Dysfunktion
COMPERA	Prospective Registry of Newly Initiated Therapies for Pumonary Hypertension
COPD	Chronic Obstructive Pulmonary Disease
COSYCONET	German COPD and SYstemic consequences – COmorbidities NETwork
COVID-19	Coronavirus disease 2019
CPC-M	Comprehensive Pneumology Center Munich
CT	Computed tomography
CTEPH	Chronic thromboembolic pulmonary hypertension
DAAB	German Allergy and Asthma Association
GIIN	German Society for Internal Intensive Care Medicine
DGP	German Respiratory Society
DKTK	German Consortium for Translational Cancer Research
DPLD	Diffuse Parenchymal Lung Disease
DWH	Data Warehouse
DZD	German Center for Diabetes Research
DZG	German Centers for Health Research
DZHK	German Center for Cardiovascular Research
DZIF	German Center for Infection Research
DZL	German Center for Lung Research
DZNE	German Center for Neurodegenerative Diseases
DZPG	German Center for Mental Health
ECFS	European Cystic Fibrosis Society
ECMO	Extracorporeal membrane oxygenation
ELD	End-Stage Lung Disease
ELF	European Lung Foundation
EMBARC	European Multicentre Bronchiectasis Audit and Research Collaboration
EPAP	European Patient Ambassador Programme
ERS	European Respiratory Society
GPP	Society for Pediatric Pneumology
IgA	Immunoglobulin A
ILH	Institute for Lung Health
IPF	Idiopathic Pulmonary Fibrosis
iPS	Induced pluripotent stem cells
ITEM	Fraunhofer Institute for Toxicology and Experimental Medicine
LC	Lung Cancer
LTx	Lung transplantation
LIS	Lung Information Service
MRI	Magnetic resonance imaging
NAKO	German National Cohort
NSCLC	Non-small-cell lung cancer
PAH	Pulmonary Arterial Hypertension
PH	Pulmonary Hypertension
PLB	Biobanking & Data Management Platform
PLI	Imaging Platform
PROGNOSIS	The Prospective German NON-CF-Bronchiectasis Registry
PROGRESS	Pneumonia Research Network on Genetic Resistance and Susceptibility for the Evolution of Severe Sepsis
RNA	Ribonucleic acid
SAB	Scientific Advisory Board
SARS-CoV-2	Severe acute respiratory syndrome coronavirus type 2
SOP	Standard Operating Procedure
TLRC	Translational Lung Research Center
TMF	Technology, Methods and Infrastructure for Networked Medical Research
UGMLC	Universities of Giessen and Marburg Lung Center

Imprint

Publisher
Deutsches Zentrum für Lungenforschung (DZL) e. V.
Head Office
Aulweg 130, D-35392 Giessen
Phone: +49 641 99-46718 / -46721, E-Mail: contact@dzl.de, Homepage: www.dzl.de

Board of Directors
Prof. Dr. Werner Seeger (Vorsitzender), 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 und Prof. Dr. Werner Seeger (Chef-Redaktion), Rogin Honar, Alina Zidaric, Staff of the Disease Areas and Platforms/Departments incl. Managers and Directors of the DZL sites

Project Management/Research
Rogin Honar, Alina Zidaric, Dr. Christian Kalberlah

Photos/Graphics
If not specified in the following: DZL e. V. or DZL partner institution; Cover: jamenpercy/stock.adobe.com; p. 6: iStock/Mladen Zivkovic; p. 8: fotolia/Sergey Nivens; p. 9: bearbeitete Abbildung aus Kammerl et *al.*, ERJ (2022)/Attribution-NonCommercial 4.0 International (CC BY-NC 4.0); p. 10: tiagozr/stock.adobe.com; p. 11: Prof. Diane Renz, BREATH; p. 12: insta_photos/stock.adobe.com; p. 13: aus Ackermann M, et *al.*, Am J Respir Crit Care Med (2022); p. 14: SneakyPeakPoints/peopleimages.com/stock.adobe.com; p. 16: iStock/Jan-Otto; p. 17: iStock/alexmak72427; p. 18: Lars Möller/Intermedial Design; p. 21: MPI für Herz- und Lungengesundheit; p. 22: iStock/TommL; p. 24: romaset/stock.adobe.com; p. 25: aus Zhu L et *al.*, Am J Physiol Lung Cell Mol Physiol (2022); p. 26: adaptiert von Stoecklein et *al.*, Lancet Respir Med (2022); p. 28: Rheinheimer S et *al.*, BMC Med Imaging (2022); p. 35: Daniela Liepelt; p. 36: Dr. Herbert Schiller und Dr. Malte Lücken; p. 37 und 40: iStock/fizkes; p. 56/57: iStock/Pheelings Media

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

SH
Schleswig-Holstein
Ministerium für Allgemeine und Berufliche Bildung, Wissenschaft, Forschung und Kultur

www.dzl.de/en

Deutsches Zentrum für Lungenforschung

Deutsches Zentrum für Lungenforschung
(German Center for Lung Research, DZL) e. V.
Head Office
Aulweg 130, D–35392 Giessen
contact@dzl.de
www.dzl.de

German Center for Lung Research (DZL)
Deutsches Zentrum für Lungenforschung (DZL)

https://www.instagram.com/dzl_de/

Klimaneutral
Druckprodukt
ClimatePartner.com/10347-1812-1001