DZL Deutsches Zentrum für Lungenforschung

DZG DEUTSCHE ZENTREN DER GESUNDHEITSFORSCHUNG

Annual Report 2021

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Foreword

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

November 14, 2011, the founding date of the German Center for Lung Research, was a day characterized by a spirit of optimism and discovery. Germany's leading scientists and clinicians in lung research, who had prevailed in a competitive process, joined forces to form a cooperative network. Since then, based on mutual trust, the DZL has been writing a success story that has been recognized several times by both international experts and high-ranking award committees. The celebrations for the anniversary or the annual meeting, which is extremely important for scientific exchange, had to be postponed from 2021 to 2022 due to the ongoing SARS-CoV-2 pandemic. Nevertheless, the DZL researchers continued to pursue the most pressing questions in their specialist areas every day in order to find new answers for improved diagnostics, therapy and prevention of lung diseases. To name just a few examples of the achievements about which you can learn more in this annual report: In the field of basic research, the involvement of macrophages in the development of chronic inflammation (p. 9) and the existence of so-called lipofibroblasts – previously known only from animal models – have also been demonstrated in humans (p. 25). Both findings provide new starting points for the development of therapies. The evidence that SARS-CoV-2 triggers fibrosis-like immune responses (p. 13) is an important building block for understanding the development and progression of COVID-19 disease and possibly post-COVID syndrome. Our researchers report on novel diagnostic possibilities in bronchial asthma (p. 7), lung adenocarcinoma (p. 21) or the use of magnetic resonance imaging in preschool children with Cystic Fibrosis (p. 26). Finally, the selected highlights of 2021 provide insight into our therapy research, such as the long-term course after lung transplantation in children and adolescents (p. 19) and report successes in triple combination therapy for CFTR modulation in Cystic Fibrosis (p. 11), the broader treatment of various DPLDs with pirfenidone (p. 15) or the use of riociguat to stimulate soluble guanylate cyclase in Pulmonary Hypertension (p. 17). Our research is always committed to the principles of medical ethics. Wherever new procedures have to be established due to a justified research interest, we work constructively on solutions, for example on the question of the use of pediatric biomaterials (p. 23).

In 2021, the DZL entered its third funding period (DZL 3.0). The central strategy is to link the established research pillars of the disease areas more closely through a horizontal exchange and thus to enrich them. The first channels of conversation have already emerged from 2021 in overarching working groups on the topics of lung-environment interactions, and microbiome, metagenomics and single cell analyses. This path is to be continued in the fourth funding period. Also as a result of the pandemic, new initiatives have been launched in the German research landscape, such as the Network University Medicine (NUM) and two new German Centers for Health Research (DZG). It will remain an important task to connect the actors along the translation chain in a meaningful way in order to create the best possible synergies through cooperation and trust in the interests of the patients. The DZG are taking an exemplary approach here by jointly using infrastructure and initiating scientific projects on cross-disease issues that need to be researched with a combined effort. We are entering this exciting future with great confidence.

We wish you stimulating and informative reading!

Giessen/Grosshansdorf/Hanover/Heidelberg/Munich in August, 2022

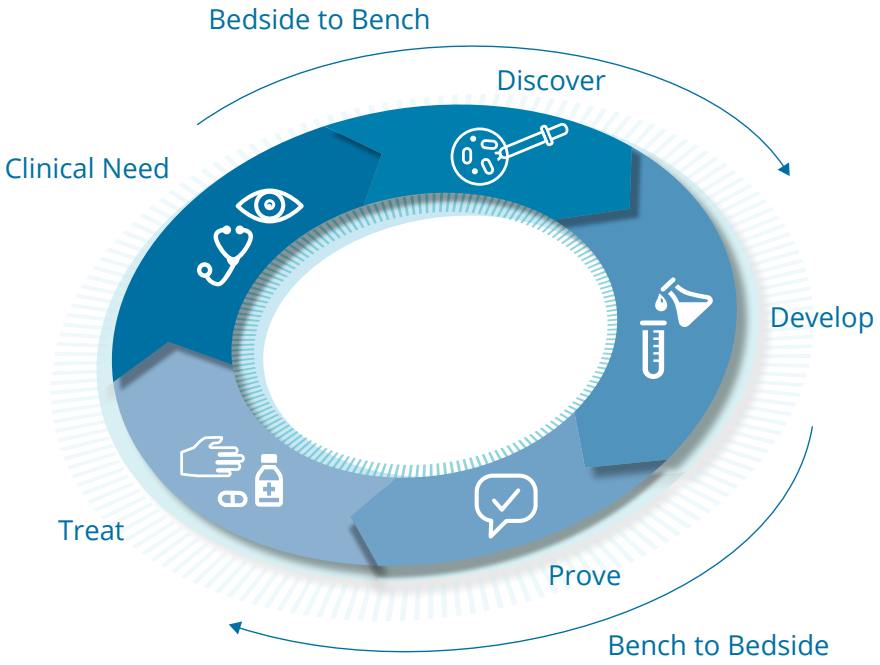
The Board of the German Center for Lung Research

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 all the 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 in order 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 in order 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 reach 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 and Allergy

Asthma is the most prevalent chronic respiratory disease in children and is also very common in adults. Although the clinical manifestations of asthma in children and adults are 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. In order to design personalized treatment approaches for asthma patients, there is urgent need to elucidate the particular molecular mechanisms underlying the various types of asthma. The decoding of such mechanisms and their translation to the individual patient is the aim of the Disease Area Asthma and Allergy of the DZL.

Goals Achieved in 2021

- ✅ 15 joint publications of several DZL sites (achieved: 30)
- ✅ 450 additional medical consultations in the ALLIANCE cohort (achieved: 568)
- ✅ Recording of Corona infections in the ALLIANCE cohort (achieved)
- ✅ Elucidation of the molecular mechanisms of epithelial immunity
- ✅ Update of the ‘toolbox’, which summarizes existing method and technology expertise in Disease Area AA and makes it available to scientists

Goals 2022

- 2 DZG-overarching publications
- 15 joint publications of several DZL sites
- 450 more medical consultations in the ALLIANCE cohort
- Further recording of asthma morbidity in the ALLIANCE cohort during the 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
- Molecular characterization of the immune response in trained immunity in primary airway epithelial cells and cell lines

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Participating DZL Partner Sites
All

Allergy or no allergy? New basophil activation test complements spectrum of routine diagnostics

A new test method improves allergy diagnostics: By optimizing the basophil activation test (BAT), a team of scientists at the Research Center Borstel has created an innovative measurement method that detects allergies quickly and precisely. Unlike conventional methods, it can detect an actual allergic reaction, not just sensitization. The team led by Prof. Dr. Uta Jappe published the results in the journal *Allergy* in December and applied for a patent. Negotiations with an industry partner are underway to bring the method into routine diagnostics.

Standard diagnostics with weaknesses

Allergists and dermatologists usually use skin prick tests and detections of IgE antibodies in the blood to investigate whether someone has come into contact with certain allergens (e.g. birch pollen). While these methods are easy to use, they only show half the truth: They detect sensitization, i.e., a reaction of the immune system. However, they do not show whether this results in clinically relevant symptoms, i.e. a real allergy. In order to prove this in unclear cases, an additional provocation test with the allergen source is currently used. However, this test can cause considerable side effects in patients, including anaphylactic shock.

An alternative to this is the basophil activation test, which mimics the allergic reaction in a test tube using a patient blood sample. Basophils are blood cells that the immune system activates as part of the allergic reaction. Until now, however, this test could not be used on a widespread basis: Since the patients' blood samples need to be processed immediately after collection, physicians without their own laboratories were unable to evaluate the BAT. In addition, there were no automated analysis procedures, which meant that the effort involved was disproportionately high. Last but not least, there was no standardized protocol for the BAT.

Optimized procedures could become routine

All these problems have been addressed by the research groups of Prof. Dr. Uta Jappe and Dr. Jochen Behrends (both from the Research Center Borstel). By optimizing the procedure, the Borstel scientists were able to establish a protocol that has the potential to replace expensive and risky provocation tests and predict the severity of the allergic reaction. The methodology reduces personnel and material costs and uses a high-throughput procedure in the fluorescence flow cytometer. A validation that has already taken place as part of a nationwide interlaboratory test showed that the protocol can be carried out independently of the device type and delivers very precise results. The optimization of the BAT has meanwhile been filed for a patent. "The possibility of using this safe and precise test in routine diagnostics led to cooperation with a company based in Germany and also aroused interest from large international companies," said Jappe. "Being able to use the BAT as a standard method in the clinic would mean great progress for the treatment of our patients."

The work in this project was partly financed by funds from the Disease Area Asthma and Allergy of the DZL and published in December in the specialist journal *Allergy*.

Further Information

Behrends J, Schwager C, Hein M, Scholzen T, Kull S, Jappe U (2021) Innovative robust basophil activation test using a novel gating strategy reliably diagnosing allergy with full automation. Allergy 76(12): 3776.

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 2021

- ✓ 20 joint publications of several DZL sites (achieved: 23)
- ✓ Continued long-term study of COSYCONET patients
- ✓ Influence of e-cigarette smoking on the respiratory tract of the fruit fly (achieved: publication)
- ✓ Comparison of the lung microbiome of smokers, ex-smokers, and never-smokers (achieved: publication)
- ✓ Identification of the immune proteasome as a biomarker and therapeutic target structure (achieved: publication)

Goals 2022

- 20 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, as well as asthma identification of physical-activity clusters in COSYCONET using AI analysis in a European comparative project (TOLIFE; Horizon 2021 Health)
- Studying the importance of small airways in mild COPD in the CAPTO cohort
- Studies of macrophage elastase regulation in pulmonary emphysema and chronic bronchitis
- Bimonthly video conferences for structured coordination

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Participating DZL Partner Sites
All

COPD and Cystic Fibrosis: viscous mucus reprograms immune cells and promotes airway inflammation

Researchers at the DZL's TLRC site have discovered how airway obstruction with viscous mucus promotes inflammatory responses that are part of the clinical picture in Cystic Fibrosis and Chronic Obstructive Pulmonary Disease (COPD). The research team showed that mucus in the airways reprograms certain cells of the immune system – called macrophages – so that they develop pro-inflammatory properties. The results of the study were published in the journal *Nature Communications*.

Suspicious mucus: does it trigger chronic inflammation?

Lung diseases such as Cystic Fibrosis and COPD are associated with severely mucus-clogged and inflamed airways. Normally, inflammation is an important part of the healing process. However, in patients with Cystic Fibrosis and COPD, persistent inflammation leads to progressive destruction of lung tissue and increased infections. The researchers were initially unable to explain the cause of the persistent airway inflammation. "Even young children with Cystic Fibrosis, in whom no infection of the lungs with pathogens can be detected, already have chronically inflamed airways. So we wondered how these chronic inflammations are triggered and suspected the mucus itself as the culprit," said Professor Marcus Mall of Charité – Universitätsmedizin Berlin.

Viscous mucus alters properties of airway macrophages

The researchers at Heidelberg University Hospital and the German Cancer Research Center (DKFZ) tested the extent to which airways clogged with viscous mucus alter certain immune cells – macrophages. Macrophages are also known as "scavenger cells". They eliminate bacteria, viruses, or dead cells and thus counteract chronic inflammation. Surprisingly, however, the researchers observed that macrophages from the airways of sick mice with severely congested airways have pro-inflammatory properties. "The macrophages from the lungs of these mice no longer fulfilled their function as scavenger cells and produced pro-inflammatory messenger substances," said Dr. Michelle Paulsen. Further experiments in which macrophages from healthy mice were treated with mucus confirmed this: as a result of the contact, the airway macrophages showed the same changes as those from the lungs of the diseased mice.

Epigenetic changes reprogram airway macrophages

To explain why airway macrophages that have come into contact with viscous airway mucus exhibit different properties than macrophages from healthy airways, the researchers took a closer look at the genetic material of the immune cells. "We were able to show that certain sections of the macrophage DNA were altered in such a way that genes for pro-inflammatory messenger substances were increasingly transcribed," said Prof. Christoph Plass from DKFZ, co-study leader together with Mall. These were not changes in the DNA sequence, but so-called epigenetic changes that influence the structure of the DNA.

Airway macrophages as a target for new therapies

The results show that mucus-clogged airways due to reprogrammed airway macrophages contribute to chronic airway inflammation and exacerbate patients' symptoms. This underscores the importance of mucolytic therapies to treat both lung diseases and opens new avenues for research. "In the future, the altered airway macrophages could serve as a target for the development of targeted therapies for Cystic Fibrosis and COPD," said Dr. Joschka Hey, a scientist at DKFZ and co-first author with Paulsen of the publication in *Nature Communications*.

Further Information

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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. 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 Cystic Fibrosis (so called CFTR modulators) is expected to significantly improve quality of life and life expectancy of persons with Cystic Fibrosis 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 (DZL) CF research program is to advance the current understanding of the pathogenesis of CF lung disease and to use this knowledge to improve CF diagnostics, develop more sensitive tools for monitoring of disease activity, and develop novel strategies for effective prevention and therapy of CF lung disease.

Goals Achieved in 2021

- ✅ First efficacy and safety study of CFTR modulators lumacaftor-ivacaftor in F508del homozygous preschool children with CF completed and evaluated
- ✅ CFTR biomarker study to investigate the attenuation of the basic CF defect using triple therapy completed and evaluated
- ✅ Establishment of the sweat secretion assay as novel CFTR biomarker
- ✅ Establishment of rheological methods to test the efficacy of novel therapies on viscoelastic properties of CF mucus
- ✅ Evaluation of the efficacy of pulmonary cell therapy for the treatment of acute airway infections with *P. aeruginosa* in a preclinical model
- ✅ Validation of novel compounds that activate the alternative chloride channels SLC26A9 identified by high-throughput screening in CF airway epithelial cells

Goals 2022

- Observational study on effects of triple combination therapy with elexacaftor-tezacaftor-ivacaftor on morphological and functional changes in CF lung disease determined by magnet 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 airway 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

New triple combination therapy improves CFTR function in airways and intestine of patients with Cystic Fibrosis

Mutations in the Cystic Fibrosis gene (CFTR gene) lead to a disturbance of the salt and water transport and thus the moistening of the mucus membranes. This basic CF defect leads to the formation of viscous mucus in various organs such as the respiratory tract, the intestine, and other affected organs and causes typical symptoms such as cough, shortness of breath, respiratory infections, and failure to thrive. Although a total of more than 2,000 mutations have been described in the CFTR gene, approximately 85 % of all patients with Cystic Fibrosis carry at least one copy of the most common mutation, F508del, which causes misfolding of the protein, leading to a severe defect in CFTR-mediated fluid transport. Recently, clinical trials demonstrated that a new triple combination therapy with the CFTR modulators elexacaftor (Elx), tezacaftor (Tez), and ivacaftor (Iva), which are small molecules designed to correct the folding defect of the F508del CFTR protein, resulted in significant improvement in clinical endpoints and sweat chloride concentration as a biomarker of CFTR function. However, the extent of restoration of CFTR function by Elx/Tez/Iva in the airway and intestine as two of the major target organs affected in patients with Cystic Fibrosis, has not been investigated to date.

In this prospective observational study at the three DZL sites Giessen, Hanover, Heidelberg and the associated partner site Berlin, a cohort of 107 patients was investigated by nasal potential difference (NPD) and intestinal current measurement (ICM) to determine the effects of Elx/Tez/Iva on CFTR function in the airways and gut of patients with Cystic Fibrosis and one or two F508del alleles in a “real-world” setting. Our study provides the first quantitative assessment of the improvement of CFTR function by triple combination therapy in the airways and gut of patients with Cystic Fibrosis and demonstrates that Elx/Tez/Iva improves CFTR function in these tissues in patients with at least one F508del allele to a level of approximately 40 % to 50 % of normal CFTR activity. This level of CFTR function is comparable to the uppermost range of CFTR activity previously observed in patients with Cystic Fibrosis and pancreatic insufficiency in residual function mutations characterized by a much milder disease course. However, we observed only weak correlations between improvement in CFTR function and short-term improvements in clinical parameters such as lung function and body mass index. On the one hand, this highlights the potential of the CFTR biomarkers ICM and NPD to detect improvements at the baseline CF level independent of short-term clinical improvements. On the other hand, it highlights that, as also emphasized in the accompanying editorial, long-term studies to determine the relationship between the improvement in CFTR function achieved by Elx/Tez/Iva and long-term clinical benefit for patients with CF are needed to fully understand the potential of these therapies.

Further Information

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Pneumonia and Acute Lung Injury

Acute lower respiratory tract infections represent an increasing public health problem worldwide, resulting in a disease burden greater than that of any other infection with mortality rates unchanged over the past 50 years. Likewise, the lack of any therapeutic treatment for the most devastating clinical course of pulmonary infection, Acute Respiratory Distress Syndrome (ARDS), and an unacceptably high mortality rate, underscore an urgent need for novel, effective therapeutic approaches. Both microbial attacks (bacteria, viruses, fungi) and non-microbial inflammatory injuries (aspiration, inhalation of toxic gases) may cause Acute Lung Injury (ALI) 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 2021

- ✓ Inhaled liposomal cyclosporine A (CsA) against SARS-CoV-2, pilot study in early symptomatic COVID-19 disease (L-CsA-I-COVID) (achieved: DZL Funding)
- ✓ Pathomechanisms of macrophage depletion and reprogramming in severe viral pneumonia to define new therapeutic target structures (largely achieved: in addition SARS-CoV-2 models have been investigated; two manuscripts in preparation)
- ✓ Development of further human-relevant infection models in the context of COVID-19 as well as for precise disease modeling (achieved: human *ex vivo* models; COVID-19 mouse models)
- ✓ Further development of clinical biomarkers to assess severity in pneumonia and pneumogenic sepsis (patents for novel markers of pneumonia and sepsis have been filed)
- ✗ ESsCOVID study – implementation postponed due to difficulties with sponsor

Goals 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 from pro-inflammatory to pro-regenerative cells
- Definition of the airway microbiome in pulmonary infection and predictive role in exacerbations of chronic lung disease such as COPD or IPF
- Implementation of the ESsCOVID study (NCT04576728, use of trimodulin in severe COVID-19 disease, phase IIa), of the phase IIa study on therapy with inhaled liposomal CsA (L-iCSA) for early COVID-19 as well as the start of validation trials for biomarkers (close cooperation with the DZIF)
- “First data available” from the GI-COVID trial

SARS-CoV-2 triggers fibrosis-like immune response and ARDS

COVID-19-induced Acute Respiratory Distress Syndrome (ARDS) is associated with prolonged respiratory failure and high mortality, but the underlying mechanisms of lung injury are still not understood to a large extent. ARDS or "shock lung" is acute damage to the alveoli with respiratory insufficiency and dyspnea (intensive care/ventilation).

In the present study, the immune response of the lungs and the accompanying pathology were examined in patients with COVID-19 ARDS using functional single-cell genome analysis, immunohistology, and electron microscopy. An accumulation of CD163-expressing monocyte-derived macrophages was found, which had fibrosis-supporting properties. Macrophages are white blood cells (leukocytes) that belong to the so-called phagocytes. As an essential part of the immune defense system, they are responsible for destroying pathogens in the body. Their receptors are adapted to the surface proteins of pathogens according to the lock-and-key principle, so pathogens and other foreign substances can be taken up and destroyed (phagocytosis). Further analysis showed a significant similarity between COVID-19-associated macrophages and macrophage populations that occur in Idiopathic Pulmonary Fibrosis.

COVID-19 ARDS was associated with clinical, radiographic, histopathologic, and ultrastructural hallmarks of pulmonary fibrosis. When human monocytes in cell culture were exposed to SARS-CoV-2 viruses, a similar profibrotic phenotype was induced in them *in vitro*. This could not be triggered by influenza A viruses or virus RNA analogues.

In summary, severe COVID-19 disease elicits not only severe inflammatory changes in the lung, but also structural fibrotic changes involving cells of the immune system.

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Further Information

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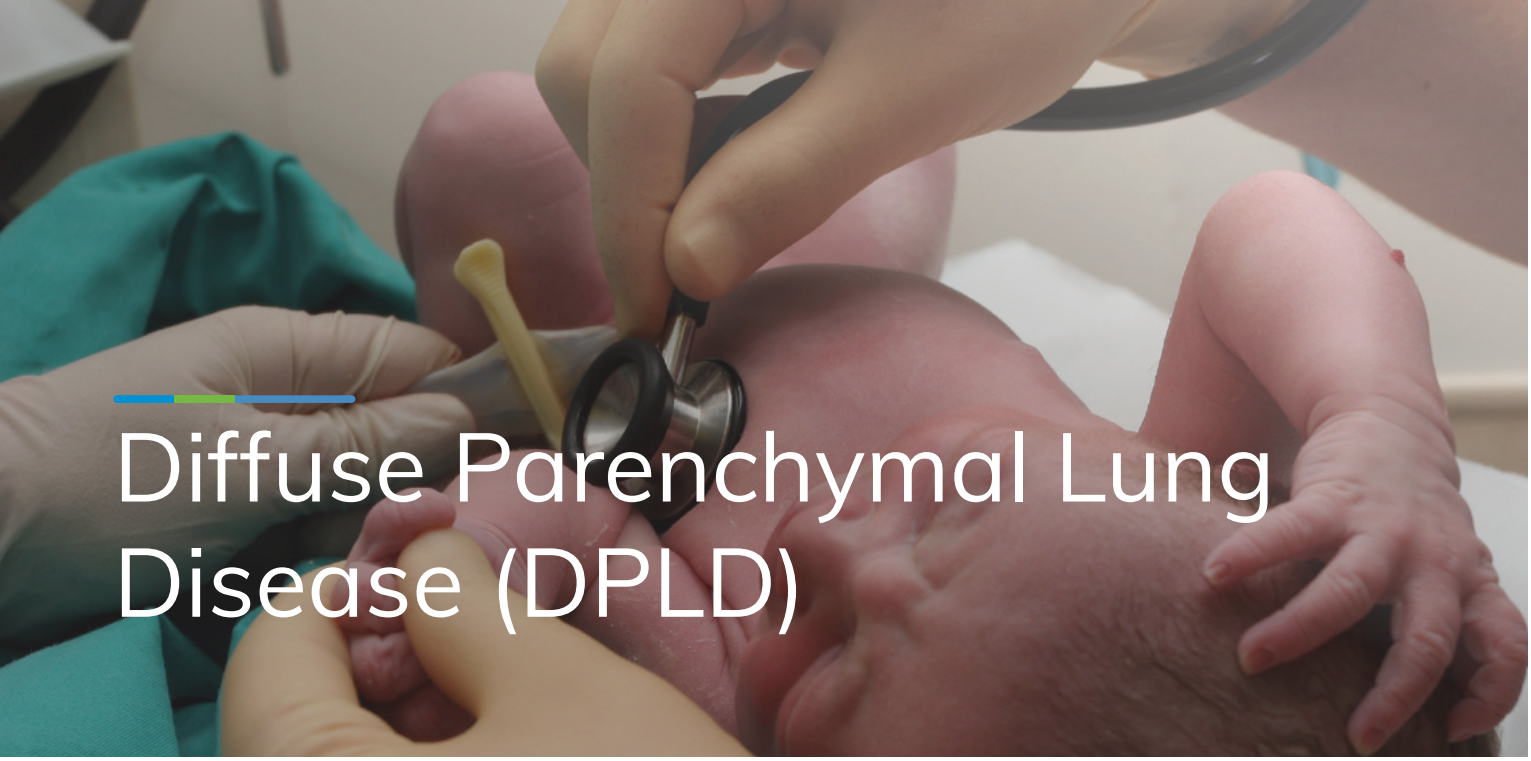

Diffuse Parenchymal Lung Disease (DPLD)

Diffuse Parenchymal Lung Diseases (DPLD) comprises more than 200 different lung diseases, most with severe courses. Although remarkably different in origin, course and genetic background – all DPLDs can lead to extensive changes in the cellular composition and interaction, a remodeling of the delicate lung scaffolding and progressive scarring. Although causes have been found for certain DPLDs, this remains unexplained for the majority of DPLDs, such as idiopathic interstitial pneumonias. As a result, only a few anti-inflammatory and antifibrotic drugs are available for treatment to date. These "antifibrotics" inhibit the progression of scarring, but they do not stop this process. Thus, the only curative treatment approach remains lung transplantation. With the goal of better understanding and treating DPLD pathogenesis and development, internationally renowned basic scientists and clinicians are collaborating across sites in the DPLD Disease Area, combining highly specialized techniques, the latest artificial intelligence methods, and clinically relevant *in vitro* and *in vivo* models. In well-defined expert areas, new insights into alveolar epithelial injury, epithelial and mesenchymal plasticity, lung scaffold structure, the role of epithelial stem cell niches, and developmentally relevant signaling pathways are being generated, and new concepts on epigenetic (re)programming and the role of infections and environmental toxins are being developed.

Goals Achieved in 2021

- ✓ Identification of important functions of non-coding RNAs for the epithelial-mesenchymal transition in DPLDs
- ✓ Collection of real-world data to influence the lung function and survival through antifibrotic therapies
- ✓ Description of the role of magnetic resonance imaging for the diagnosis of bronchopulmonary dysplasia and its morbidities
- ✓ Characterization of the role of the Wnt signaling pathway in the development of senescence in the alveolar epithelium

Goals 2022

- Analysis of mechanistic relationships between COVID-19 and DPLD development
- Development and analysis of overarching models and mechanisms on DPLDs 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)

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BREATH, CPC-M, TLRC, UGMLC

Pirfenidone may also help with other fibrotic lung diseases – not just IPF

Pirfenidone has been approved for patients with Idiopathic Pulmonary Fibrosis (IPF) for several years and slows the decline in lung function and prolongs survival. However, for patients with other forms of DPLD, many of whom also share the so-called usual interstitial pneumonia (UIP) pattern and progressive-fibrosing character with IPF, no therapeutic offers have existed to date. Against this background, the DZL conducted a multicenter, double-blind, randomized, placebo-controlled, investigator-initiated phase IIb study in 17 German centers. 127 patients with fibrotic non-specific interstitial pneumonia (fNSIP), chronic exogenous allergic alveolitis (cEAA), collagenosis-induced DPLD (CVD-ILD), and asbestos-induced pulmonary fibrosis were included. Disease progression despite conventional therapy (e.g. steroids) was required as a major inclusion criterion and defined as a greater than 5 % annual decline in forced vital capacity (FVC) in at least 3 pulmonary functions 24 to 6 months before inclusion. Patients received either 3 x 801 mg pirfenidone or placebo over a 48-week period. The primary endpoint was absolute change in FVC as determined by a RANK ANCOVA procedure. In addition, several sensitivity tests of the primary end point were performed, including after application of various imputation models and analysis of the slope of FVC. Finally, a number of other lung function and gas exchange parameters, exercise capacity tests, and patient-relevant parameters were determined. The study was stopped after enrollment of 127 patients following an interim analysis due to slow recruitment rate. Analysis of the primary study endpoint revealed a significantly lower decrease in FVC in the verum versus placebo group (p=0.043). This observation was also verifiable using various imputation rules and also after analyzing the slope of the FVC drop. In addition, a comparable effect of pirfenidone therapy on the decrease in diffusion capacity and, significantly, on the decrease in the distance covered in the 6-minute walking test could be determined purely numerically (but not statistically significant). One patient in the verum group died of non-pulmonary causes during the observation period, five patients in the placebo group died, three of them of respiratory causes. In general, pirfenidone therapy was well tolerated: with the exception of known gastrointestinal side effects, all recorded side effects were approximately equally distributed between verum and placebo. Infections were slightly less frequent in the verum group. Although the premature termination of the study complicates the interpretation of the data and causes some uncertainties, the results of our study suggest that use of pirfenidone in non-IPF patients with progressively increasing pulmonary fibrosis as in IPF leads to attenuation of FVC and a decrease in carbon monoxide transfer factor (TLCO), as well as loss of exercise capacity. The observed spectrum of side effects is in line with observations in IPF and appears moderate given the severity of the pulmonary disease. Our results are also supported by observations with pirfenidone in another clinical trial (uILD) and with nintedanib in two other trials (Senscis and Inpulsis) conducted at the same time.

Further Information

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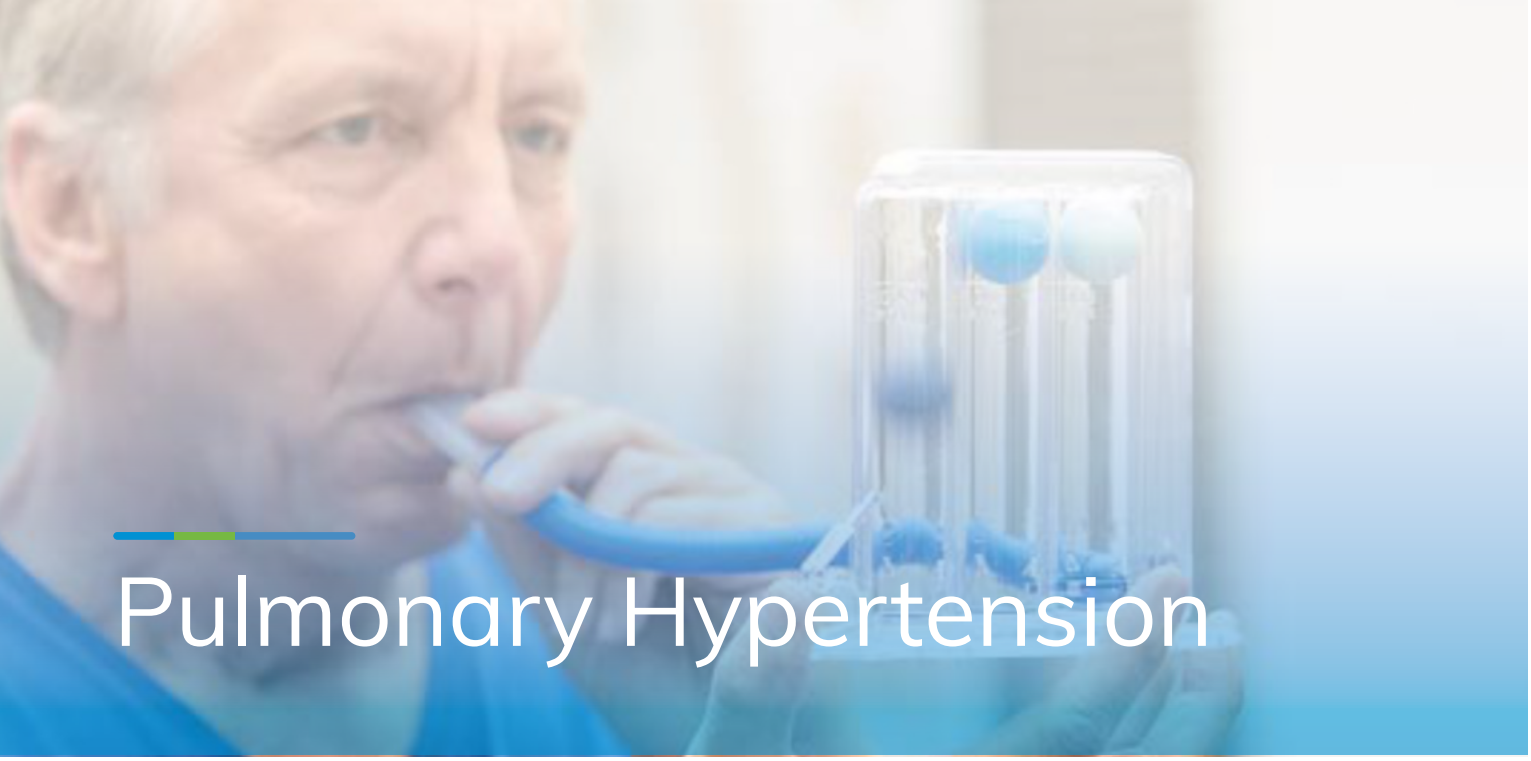

Pulmonary Hypertension

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 its remodeling. All this leads to a severe loss of the cross-sectional area of the vessels and an increase in right ventricular after load. Currently available PH therapy relies on vasodilators that can be administered alone or in combination. 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 2021

- ↔ Epigenetic studies of vascular cells in Pulmonary Hypertension. This project will be continued in 2022 to further study the epigenetic changes.
- ✓ Clinical functional and imaging studies on the role of the right heart in various forms of Pulmonary Hypertension
- ↔ Kinase profile from circulating cells from PAH patients – In this project, continuous isolations of circulating cells in various forms of PH are taking place. Therefore, this goal will continue to be pursued in 2022.
- ✓ Conduct of preclinical experiments to test anti-proliferative substances in Pulmonary Hypertension
- ✓ Evaluation of databases to validate new risk-adjusted therapy strategies of environmental influences

Goals 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

Switching the medication of Pulmonary Hypertension from phosphodiesterase inhibitors to the soluble guanylate cyclase stimulator – the REPLACE study

Both stimulation of the soluble guanylate cyclase signaling pathway and inhibition of a component of it (phosphodiesterase [PDE]-5) are used in the therapy of Pulmonary Hypertension. For patients who do not respond satisfactorily to PDE-5 inhibitors (sildenafil, tadalafil), replacement therapy with the sGC stimulator riociguat may be an option. This was tested in a multicenter international clinical trial, the so-called REPLACE study, with participation of several DZL sites (NCT02891850). REPLACE is thus the first randomized controlled study in patients with Pulmonary Arterial Hypertension (PAH) to investigate switching within the same signaling pathway as well as the first head-to-head study of approved PAH therapies.

For this purpose, patients with ongoing PDE-5 inhibitor therapy who had an intermediate risk of mortality ("estimated 1 year mortality", European Society for Cardiology guideline, Galie et al, ERJ 2015) were recruited. Participants received the sGC activator riociguat instead of existing PDE-5 inhibitor therapy or continued existing therapy unchanged. A total of 224 data sets were analyzed. 41 % of participants in the riociguat group showed clinical improvement within 24 weeks, compared with only 20 % in the control group (continuation of PDE-5 inhibitor therapy). Deterioration (measured as hospitalization) was seen in one patient in the riociguat group and 9 % of patients in the PDE-5 inhibitor group.

Thus, in summary, switching therapy from PDE-5 inhibition to activation of the same pathway by riociguat may represent a strategic option for the treatment of Pulmonary Hypertension. By optimizing the NO-sGC-cGMP pathway by switching from PDE5i to riociguat, patients may remain on monotherapy or dual-combination therapy, delaying the addition of further therapies to a later stage.

Further Information

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https://www.replace-study.com

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End-Stage Lung Disease

Acute and chronic lung diseases can lead to terminal lung failure. If ventilation is not sufficient, extracorporeal membrane oxygenation (ECMO) and lung transplantation (LTx) are available. When ECMO is used, the lungs can potentially regenerate (also in the case of influenza or COVID-19). In cases of chronic lung injury, LTx remains the only therapeutic option. However, it is possible in only a few patients due to organ shortage and multiple contraindications (e.g. lung tumors). Moreover, the long-term prognosis after LTx is still poor in terms of morbidity and mortality due to frequent chronic lung allograft dysfunction (CLAD).

Therefore, current research aims at improving the hemo- and biocompatibility of ECMO systems and at developing an intracorporeal "biohybrid lung". In the context of LTx, pre- and post-operative care is being optimized, in particular to detect CLAD at an early stage, to classify it and to treat it individually. The shortage of organs is being countered by establishing xenotransplantation and tissue engineering. The latter is made possible by considerable progress in the differentiation of human induced pluripotent stem cells (iPS) into various lung cell types. Thus, decellularized lungs will be colonized, as well as new lungs produced by 3D printing. The ex *vivo* perfusion systems used in LTx to reduce ischemia-reperfusion injury will be used to establish innovative therapies, e.g. stem cell therapies with correction of gene defects as well as effective high-dose chemotherapies for tumor treatment in explanted lungs.

Goals Achieved in 2021

- ✓ First *in-vivo* analyses of the biohybrid lung in an animal model
- ✓ Studies on innovative prophylaxis, diagnostics, therapy, and prognosis of CLAD
- ✓ Establishment of the *ex-vivo* setting for xenotransplantation
- ✓ Optimization of the production of iPS-based pulmonary cells for therapy and as a disease model, including COVID-19
- ✓ Evaluation of a first pulmonary 3D print template
- ✓ Indication and results of lung transplantation in COVID-19

Goals 2022

- Establishment of *ex vivo* therapy for Pulmonary Hypertension using iPS-based endothelial cells
- CLAD: Cathepsin-B as a biomarker and therapeutic target
- Xenotransplantation: Drug targeting by *ex vivo* lung perfusion (EVLP)
- Biohybrid lung in the large animal model
- Unilateral lung transplantation for potentially reversible lung disease
- Establishment of an *ex vivo* model for evaluation of pulmonary phage therapy

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Indications and long-term outcome after lung transplantation in children under twelve years of age

Lung transplantation is an established treatment option for children and adolescents with severe and progressive lung disease without other treatment alternatives. However, due to low patient numbers worldwide, experience is very limited compared to adults. Cystic Fibrosis (CF) is still the most common indication for lung transplantation in children and adolescents, but the proportion has steadily decreased in recent years due to increasingly improved treatment options. In contrast, the number of transplantations of critically ill young children with other underlying diseases such as Pulmonary Hypertension (PH) or childhood interstitial lung disease (ChILD) has steadily increased. This shift is accompanied by a simultaneous reduction in the age at the time of transplantation from adolescence towards children, infants and even babies. The "new" indications and the young age pose new challenges for the treating physicians. For example, children who are severely ill before transplantation, some of whom require ventilation, as well as heterogeneous and complex clinical pictures with additional involvement of other organ systems should be mentioned. Another important point is the increased vulnerability of the child's body to potentially toxic drugs as well as diagnostic procedures involving radiation.

In a retrospective study, DZL researchers have now investigated the clinical status before transplantation and the postoperative course of children under 12 years of age over a period of 16 years and compared it with the results of adolescents over 12 years of age. Of the 1,766 patients transplanted at Hannover Medical School from 2005 to 2021, 126 were younger than 18. Of these, 42 children under 12 and 75 adolescents 12 years and older were included in the analysis. In the group of children, the indications ChILD and PH were significantly more frequent than in the group of adolescents, where CF was the most frequent indication. Children required mechanical ventilation significantly more often than the adolescents before transplantation, and they also required mechanical pulmonary or cardiopulmonary support more often during and after transplantation. Furthermore, children required significantly longer ventilation and intensive care after transplantation than adolescents. Organ survival 1, 5 and 8 years after transplantation was 91 %, 72 %, and 68 % in children and adolescents combined and tended to be better in the children's group (90 %, 80 %, and 80 %) than in the adolescent group (92 %, 69 %, and 62 %), but was not statistically significant. At 8 years after transplantation, 87 % of the children and 69 % of the adolescents were still alive. There were no differences with respect to acute and chronic rejections and infections requiring inpatient treatment. In summary, it could be shown that children are in a more critical state than adolescents at the time of transplantation. Nevertheless, the long-term outcome in this age group even tends to be better than in adolescents, which is why this therapy option should be considered more frequently in this age group.

Further Information

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Lung Cancer

Lung Cancer is among the most common types of cancer in Germany. The high mortality rate is often due to diagnosis at a late stage: 40 % of Non-Small Cell Lung Cancer (NSCLC) patients present with metastases. Advances in molecular tumor analysis have led to new opportunities to develop targeted therapies that act on specific molecular targets of cancer cells. Besides chemotherapy and targeted therapy, immunotherapy is the third main pillar of systemic therapy. Immune checkpoint inhibitors unmask the cancer cells and enhance the body's immune response against malignant cells. In precision medicine, one major research goal is to identify non-invasively obtained biomarkers that predict response or potential failure to treatment in real time, such as the evidence of genetic tumor material in blood samples (liquid biopsy). Research is increasingly focusing on the tumor microenvironment to explore the mechanisms of tumor development and resistance to therapy. Its cellular components are in a lively exchange. They are influenced by the cancer cells, reprogrammed, and ultimately actively promote tumor development. Furthermore, in a functional research approach, individual patient-derived cancer cells are examined in a test tube for drug response. In the future, the interplay of these datasets will enable the tailoring of therapy to each individual patient in what is known as precision medicine.

Goals Achieved in 2021

- ✓ Novel preclinical models were generated to assess the effect of immunotherapy treatments on the tumor microenvironment.
- ✓ Publication of new insights into the relative contribution of distinct subsets of macrophages, fibrocytes and T cells to lung tumor growth and metastasis
- ✓ Identification of novel biomarkers and therapeutic targets that are aimed at the reprogramming of changes in the metabolic tumor adaptation
- ✓ Novel molecular risk factors in oncogene-driven NSCLC were identified and published.
- ✓ Publication of new insights in relation to the impact of functionally diverse p53 mutations on therapy resistance

Goals 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

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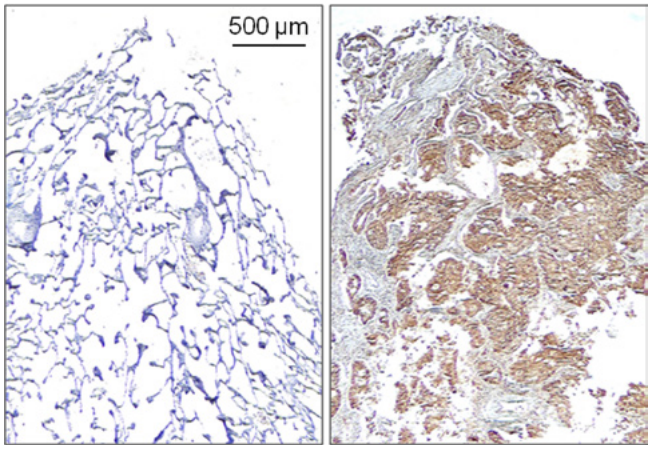
All

Lung adenocarcinoma: Molecular biomarkers allow prognoses of disease progression

Adenocarcinoma is the most common form of Lung Cancer. It is estimated that about 1 million people worldwide die from the disease each year. If the tumor is surgically removed at an early stage, there is a chance of cure. However, individual patients' chances of survival vary greatly. Therefore, DZL scientists at the Munich site investigated if certain characteristics of the removed tumor tissue – so-called molecular biomarkers – allow prognoses about disease progression.

In a new study, they examined the removed tumor tissue of 200 patients for the presence of such biomarkers. They knew that certain proteins are typically found in cancer cells at high levels – probably, because they promote tumor growth. Using an immunoassay, the researchers determined the levels of six of these proteins. The immunoassay uses labelled antibodies that selectively bind to these proteins and make them visible. The researchers also examined whether the patients' tumor cells contained larger amounts of fragmented genetic material (DNA). After the tumor was removed, all patients were followed for an additional 5 years to determine whether the studied biomarkers allowed conclusions to be drawn about patient survival.

The analysis of the study showed that the examined patients could be divided into two groups. In the tumor tissue of the first group (60 % of the patients), the researchers found four cancer-typical proteins whose levels were strikingly high. Only half of this group was still alive after five years. In the second group (40 %), the levels of the four cancer-typical proteins were not greatly increased, but a large amount of fragmented DNA was found in the cells of the tumor tissue. This group of patients had higher survival rates – after 5 years 70 % of them were still alive.



Left: Normal lung tissue; **Right:** Lung adenocarcinoma
The image shows an immunoassay that the researchers used to detect a protein typical of cancer in the tissue of an adenocarcinoma (brown staining). The protein could not be detected in normal lung tissue.

The seven biomarkers investigated in the study may help to reliably assign patients with adenocarcinoma to one of two groups - one with a lower chance of survival and one with a higher chance of survival. To help physicians assign patients to one of these two groups, the researchers developed a scoring system and instructions for using the biomarkers. Combined with tumor stage information, the new biomarkers may help physicians to make more accurate prognoses about the life expectancy of patients and to tailor the further course of treatment more individually.

Further Information

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Biobanking & Data Management Platform

The aim of the DZL Biobanking platform is the SOP-based acquisition, processing, collection, storage, and administration of biomaterials as well as the collection of associated clinical data from the most diverse pulmonary disease areas in compliance with all necessary legal standards. Scientists within the DZL, but also external cooperation partners, should be able to access biosamples and data easily and in compliance with the rules. In terms of quality management, the harmonization of patient information documents for informed consent, data protection concepts, standardized work processes with regard to quality control, and data management is a central concern of all DZL locations.

Goals Achieved in 2021

- ✓ Implementation of a QM circle for the preparation of certification/accreditation of biobanks (ISO20387), establishment of a central contact point for ethics issues
- ✓ Use of the DZL data warehouse (DWH) as a service infrastructure
- ✓ Integration of further databases, cohorts and registries into the DZL DWH, improvement of the data quality and data depth
- ✓ Collection of biosamples and associated clinical data
- ✓ Training with regard to biobank-relevant topics

Goals 2022

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

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Broad consent for pediatric biobanking at the DZL – a template for a two-step informed consent process for the use of genetic data

Children, as a particularly vulnerable group, have long been excluded from non-therapeutic medical research. In 2009, with the publication of the OECD Guidelines for Human Biobanks and Genetic Research Databases (HBGRDs), pediatric biobanking came into focus, and with it the requirement to obtain the consent of legally competent minors for the scientific use of their samples and data. Pediatric biobanking of so-called residual material undoubtedly implies key challenges for pediatric research: on the one hand, the often reduced random-sample size and sample volume in pediatric patients, and on the other hand, the minimization of risk by using residual material from the clinical context.

Similarly, the use of pediatric biospecimens for genetic research has been discussed for years. In contrast to broad consent (BC) for adults, consent to genetic research with pediatric biospecimens and the possibility of incidental findings resulting from it may have implications not only for the future of the child concerned, but also for that of his or her siblings and the entire family.

Following the texts of the Association of Medical Ethics Committees (AKEK), the DZL developed a template for a two-step procedure for information and consent of minor patients in order to inform parents, children and their families precisely about possible consequences of the generation of genetic data for research purposes and the possibly required procedure in case of incidental findings. The basic idea was that at the time of information and consent – a possibly upsetting and stressful clinical situation for both parents and children – there can hardly be sufficient understanding of the consequences of using biomaterial for genetic research. The presented two-stage procedure differentiates between genetic data that have already been generated in the context of care (basic broad consent) and genetic data that are newly generated for research purposes. It can be assumed that for genetic analyses in the context of care, an explanation of their consequences has been provided. Consent to the use of these data for research purposes is given in the course of basic broad consent in accordance with general information on broad consent for the use of biospecimens and data from the treatment context. Additional patient information will be handed out for the generation of genetic data for research purposes. This explicitly states that the consent can be decided without time pressure or stress. In this way, the DZL's two-step consent model for pediatric biobanking combines aspects of tiered and familial consent.

The clear separation between consent to the use of existing genetic data (basic broad consent) and consent to the generation of new data for research purposes also ensures clarity with regard to the use in the use-and-access procedure for data and biospecimen release. A positive side effect for the biobank can be a lower rejection rate for the generation and use of genetic data, which is after all undifferentiated.

It is planned to pilot the implementation of the described procedure and to evaluate the feasibility of the required workflows. This evaluation will be flanked by a questionnaire study on the understanding and acceptance of the procedure by those affected.

Further Information

Gesine Richter, Karoline I. Gaede and DZL-Platform Biobanking and Datamanagement Pediatric Broad Consent in the German Center for Lung Research (DZL) – a template for a two-step procedure for genetic data use. European Biobank Week "Biobanking for our future – opportunities unlocked", Presentation on 10.11.2021

Imaging Platform

A broad spectrum of innovative imaging techniques in microscopy and radiology is now available to scientists at the DZL to gain new insights into the development and evolution of lung diseases, to test drug efficacy and to support the development process of new drugs. The imaging platform ensures the availability of various imaging technologies within the DZL and promotes the use of imaging for research and translation. “Imaging” in this context is understood as the interaction of imaging techniques of different modalities of different resolutions and different scales in preclinical, translational, and clinical settings.

Artificial Intelligence (AI) in imaging has the potential to improve the diagnosis and treatment of patients with lung diseases. 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. This will result in new and wider-ranging opportunities to also merge these imaging biomarkers with clinical, biological, and genomic information and again share them using AI techniques. The development of the necessary AI algorithms and analysis programs is still in its infancy, but they will make an important contribution to personalized medicine in the near future.

Goals Achieved in 2021

- ☑ 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 2022

- All of the above work packages will be pursued as goals for 2022

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Combination of different microscopic procedures proves existence of lipofibroblasts in the human lung

Around 40 different cell types are involved in building the human lung. To understand the development of lung diseases, researchers first study the function of these cells in animal models. They then check whether the results can be transferred to humans. For example, they have to prove that cell types found in the lungs of animals actually occur in humans. To do this, they use microscopic techniques such as fluorescence or electron microscopy. In the past, researchers had not been able to clearly prove the existence of special connective tissue cells – lipofibroblasts – in human lungs. DZL scientists at Hannover Medical School have now combined known microscopic detection methods and were the first to succeed in clearly visualizing the cells.

For the study, the researchers examined samples from the lung tissue of patients with pulmonary fibrosis or emphysema, as well as unchanged lung tissue from patients with lung cancer. They prepared the tissue for further microscopic examination and made wafer-thin sections. Lipofibroblasts are characterized by special molecular properties, among other things. The researchers marked these in such a way that they became visible as colored dots on the tissue sections under the fluorescence microscope. This enabled them to identify the locations in the tissue that probably contained lipofibroblasts. However, the resolution of the fluorescence microscopic images was too low to allow them to identify characteristic cell structures of the lipofibroblasts. Therefore, they detached the areas that had been identified under the light microscope from the section and additionally examined them with an electron microscope. With about 500 times the resolution, they discovered that the labeled cells contained fat droplets and were in close proximity to collagen fibers, which clearly identified them as lipofibroblasts. By combining fluorescence and electron microscopy, the researchers thus clearly demonstrated the presence of lipofibroblasts in the human lung.

DZL scientists Dr. Julia Schipke and Prof. Christian Mühlfeld succeeded in imaging lipofibroblasts in human lung tissue

This discovery fills an important gap in lung research and could help develop new therapies for various lung diseases. Using animal models, lipofibroblasts have been shown to play a role in lung development and are also indirectly involved in the development of pulmonary fibrosis. If the results from animals can be transferred to humans, lipofibroblasts could soon become a target for the development of new therapies.

Further Information

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Magnetic resonance imaging in preschool children with Cystic Fibrosis

Cystic Fibrosis is a congenital, incurable multi-organ disease associated with progressive damage to the lungs. Doctors often use imaging techniques such as X-rays or computed tomography (CT) scans to detect lung damage and assess the course of the disease. However, both procedures expose patients to a dose of radiation, which is particularly concerning for infants and children. Therefore, DZL scientists at Heidelberg University Hospital are investigating to what extent magnetic resonance imaging (MRI) is suitable as a radiation-free imaging method for assessing the course of the disease in Cystic Fibrosis.

In a new clinical study of about 100 children aged 0-4 years, researchers explored two questions: Can annual MRI exams map changes in lung tissue in young children? And can MRI detect the impact of starting therapy early? The participating children were diagnosed with the disease at different times. Some had participated in newborn screening and were diagnosed before symptom onset. The remaining children already had symptoms suggestive of Cystic Fibrosis. Based on the early screening, the first group could be treated with preventive inhalation therapy. In the second group, therapy was given only after the onset of symptoms.

The evaluation of the study showed that MRI is precise enough to track the progression of Cysric Fibrosis in preschool children. For example, increasing changes in the lungs were evident over the first four years of life. The bronchial walls became thicker over the years and ventilation of certain areas of the lungs decreased as the airways became blocked with mucus.

Furthermore, the study confirmed the advantages of an early start of therapy. If the disease was detected and treated during the newborn screening before the first

MRI scans of preschool children have allowed physicians to map the progression of CF and the benefits of newborn screening

symptoms appeared, changes in the lungs were less pronounced than if the children were treated only after symptoms appeared. The researchers conclude that starting therapy at the asymptomatic stage keeps the disease at a low level, but cannot stop its progression.

With their work, the researchers showed that MRI scans provide important information to adjust patients' treatment in time and offer tailored therapies. In the future, they plan to use MRI in clinical trials to explore the effectiveness of new therapies for Cysric Fibrosis. This could include investigating whether a new group of drugs – CFTR modulators – can stop or slow the progression of the disease.

Further Information

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DZL Technology Transfer Consortium

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Dr. Peter Stumpf
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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 exploitation of their research findings. It consists of representatives of the technology transfer organizations of all DZL partner institutions as well as representatives of the DZL, Prof. Dr. Werner Seeger (Chairman of the DZL Executive Board), who acts as scientific advisor, and Franziska Hauptkorn, coordinator of the DZL site CPC-M (Munich).

In the run-up to the 2020 DZL Annual Meeting, the Consortium reviewed nearly 300 abstracts for patent-relevant content.

The Consortium provides DZL members with the following services:

- Abstract screening prior to DZL meetings
- An abstract screening "hotline" to request as needed
- Review of the contents of exploitation agreements
- Targeted consulting and advisory services to prepare scientists for scientific reviews by the Federal Institute for Drugs and Medical Devices (BfArM), in order to avoid potential procedural errors beforehand

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, the DZL allocates a portion of its budget to innovative clinical trials based on initiatives by DZL scientists ("Investigator Initiated Trials"). This funding enables researchers to react to the latest research developments in their field and to pursue these as quickly as possible for the benefit of patients. The funds are to be understood as start-up capital, which enables a rapid transfer of the latest findings into first-in-human clinical trials.

In 2021, the total funding volume for the current trials was EUR 1.36 million. In addition, funding for two further trials was approved, with a total funding volume of EUR 523,000 for the period up to the end of 2023.

In a second funding line to finance the preparation and drafting of applications for clinical trials, five such applications were approved in the reporting year, each in the amount of EUR 30,000. The aim of this funding line is to use the prepared full proposals later on for an application to the DZL as well as to other funding bodies, e.g. the DFG or the BMBF.

In addition to DZL-funded trials, DZL scientists are involved in more than 250 clinical trials on novel diagnostic and therapeutic approaches in lung diseases. Most of these trials are conducted in cooperation with and funded by the pharmaceutical industry.

Northern German lung cancer centers launch the HANSE study

In early summer 2021, the largest German program to date for the early detection of lung and cardiovascular diseases started at three DZL sites in northern Germany with more than 12,000 test persons. In this program, women and men aged 55-79 are invited to take part in a free lung check who, as smokers and ex-smokers, are at increased risk for lung tumors. Up to 5,000 participants will be examined free of charge in a modern low-dose CT, which will be provided in a mobile study truck, alternating between the three DZL sites in Hanover, Lübeck and Grosshansdorf. Prominent patron of the HANSE study is Dr. Eckart von Hirschhausen.

In this study, the feasibility and effectiveness of a model-based versus a conventional risk assessment for lung cancer will be tested, as especially individuals with an increased risk of lung cancer will benefit from a screening program. At the same time, possible other lung or heart diseases will be investigated based on specific changes in the CT. The image data are analyzed by experienced radiologists, supported by state-of-the-art image analysis software with artificial intelligence. Markers such as changes in the blood will also be used for early lung cancer detection.

As expected, early-stage lung cancer was already detected in several study participants during the first months of the study. Lung tumors that are detected early have a better chance of being cured. They are often still small, localized and have not yet spread. This means they can be successfully treated. Minimally invasive surgery can usually cure patients completely.

When the planned 5,000 subjects start the one-year follow-up of the study in summer 2022, statistically about 70 lung cancers will already have been detected. How many of the subjects will then have quit smoking as a result of their new knowledge about their lung and heart health is just one of the study's many questions.

Further Information

Vogel-Claussen J, Lasch F, Bollmann BA, May K, Kuhlmann A, Schmid-Bindert G, Kaaks R, Barkhausen J, Bohnet S, Reck M. Design and Rationale of the HANSE Study: A Holistic German Lung Cancer Screening Trial Using Low-Dose Computed Tomography. Rofo. 2022 Aug 2.

Investigator-Initiated Trials supported with DZL-Funds

Senior Scientist(s)	Disease Area	Participating DZL Partner Sites	Title
Herold S / Welte T	Pneumonia and Acute Lung Injury	BREATH, UGMLC	GI-Hope: GM-CSF Inhalation to improve Host defense and Pulmonary barrier restoration in patients with pneumonia-associated ARDS
Kreuter M / Vogelmeier C / Herth F	COPD	TLRC, UGMLC	ExperTENTION: Exploring efficacy of periodontal treatment on systemic inflammation and for prevention of exacerbations in patients with COPD
Reck M / Ammerpohl O / Barreto G	Lung Cancer	all	EmoLung: Monitoring of patients with NSCLC – epigenetic analysis of liquid biopsies and RNA-analysis in exhaled breath condensates
Schulz H / Meiners S / Vogelmeier C / Behr J	COPD	CPC-M, UGMLC	PBMC: Proteasome Function as a Biomarker for COPD
Seeger W / Ghofrani A / Gall J	Pulmonary Hypertension	BREATH, UGMLC	Right Heart 3: Influence of specific PAH medication on right ventricular function in patients with pulmonary arterial hypertension
Vogel-Claussen J	Imaging Platform/ Pulmonary Hypertension	BREATH, CPC-M, UGMLC, TLRC	Change MRI: Phase III diagnostic trial to demonstrate that functional lung MRI can replace VQ-SPECT in a diagnostic strategy for patients with suspected CTEPH
Zabel P / Herth F / König I / Rabe K / Welte T	COPD	ARCN, BREATH, TLRC	PLBV: Evaluation of non-invasive pursed-lip breathing ventilation in advanced COPD
Sommerburg O	Cystic Fibrosis	ARCN, BIH, TLRC, UGMLC	ANAKIN: A phase IIa trial to evaluate safety and efficacy of subcutaneous administration of anakinra in patients with cycstic fibrosis
Eichhorn M / Savai R	Lung Cancer	TLRC, UGMLC	Neomun Trial: Neoadjuvant anti-PD-1-immunotherapy in resectable NSCLC
Behr J / Mertsch P / Ringshausen F / Rademacher J	Bronchiectasis Disease	BREATH, CPC-M, UGMLC	Eradicate: Inhaled Levofloxacin in adult bronchiectasis patients with early asymptomatic Pseudomonas aeruginosa infection
Kneidinger N / Yildirim A Ö / Hecker M	End-Stage Lung Disease	CPC-M, UGMLC	CatBOS: Cathepsin-B (CatB) as a new biomarker and therapeutic target for early bronchiolotis obliterans syndrome (BOS) after lung transplantation
Vogel-Claussen J / Bohnet S / Reck M	Lung Cancer	ARCN, BREATH	HANSE study: Holistic Implementation study assessing a Northern German interdisciplinary lung cancer screening effort

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)

DZL Collaborations, Partnerships, and Networks

In 2021, within the framework of the German Center for Lung Research (DZL), approximately 270 scientists and their working groups from 29 university and non-university research institutions and hospitals collaborated at five German DZL sites and other sites of the associated partners. Across the sites and the entire network of external partners, an intensive exchange took place between the DZL researchers in order to best achieve their common objective – to investigate and combat lung diseases. Along with weekly telephone conferences and numerous regular meetings of the working groups, committees and administrative units, the **DZL Annual Meeting** should be highlighted for this purpose, although in 2021 it had to be postponed to the following year for the first time in the history of the DZL due to the COVID-19 pandemic (see p. 39).

Since its foundation, the German Center for Lung Research has been part of several networks for research into various lung diseases and is associated with other organizations that contribute to the realization of the research projects. The expansion and development of **partnerships in the fields of science and research, promotion of young scientists, patient information and interests, clinical studies, industry, and educational work** continue to be actively pursued. Numerous **collaborations on a national and international level** strengthen the position of the DZL as an outstanding institution and the largest German research network in the field of lung research.

The DZL cooperates closely with the **Lung Information Service (LIS)**, based at Helmholtz Zentrum München, and supports the provision of easy-to-understand information from research and clinical practice on lung diseases. Together, the DZL and the LIS focus on the interests of patients. You can find out more about the joint activities in the chapter “The public face of the DZL” as from p. 38 of this annual report.

Ever since the foundation of the DZL, there has been a close cooperation with the network **COSYCONET (German COPD and SYstemic consequences – COmorbidities NETwork)** through scientists belonging to both institutions. In the Germany-wide registry for the pulmonary disease COPD, the third most common cause of death worldwide, 29 study centers are involved. As part of the cohort study COSYCONET, a long-term observation of more than 2,800 COPD patients is being conducted. The studies will provide new data on the development of the disease, its level of severity, and its comorbidities. COSYCONET has a biobank, an image database, and phenotypic data at its disposal that serve as the basis for the various subprojects. COSYCONET has been integrated into the DZL as an associated partner since 2016.

Since the beginning of 2013, **CAPNETZ (German Competence Network for Community Acquired Pneumonia)** has been an associated partner of the DZL. The Competence Network aims to gain new insights into the development and course of community-acquired pneumonia (CAP), to develop improved diagnostic standards and therapies, and to strengthen education and prevention. As a potentially life-threatening disease, pneumonia is responsible for up to 20,000 deaths per year in Germany alone. With the largest epidemiological study in Europe, comprising more than 12,000 patients suffering from CAP, and the world‘s most comprehensive database on community-acquired pneumonia, the DZL has gained a strong partner in this field. The DZL has also expanded its network with scientists and study centers in Europe. For example, CAPNETZ is involved in **PREPARE (Platform for European Preparedness Against (Re) emerging Epidemics),** a program funded by the European Union to carry out research into infectious diseases with epidemic potential.

Registries and patient cohorts are of great and increasing importance for translational research at the DZL. Large cohorts and registries are brought into the DZL by associ-

ated institutions. For instance, together with CAPNETZ, the DZL has since 2015 been involved in the establishment of the bronchiectasis registry **PROGNOSIS (The Prospective German Non-CF-Bronchiectasis Registry**) and the pediatric CAP cohort **Ped-CAPNETZ**. PROGNOSIS is also part of the EU-funded European registry **EMBARC (European Multicentre Bronchiectasis Audit and Research Collaboration)** and has been an associated partner of the DZL since the turn of the year 2016/17. In addition, DZL scientists are actively involved in many other registries and cohorts, such as the Pulmonary Hypertension registry **COMPERA (Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension)** or the German National Cohort (NAKO)**.**

The **German National Cohort (NAKO)**, launched in 2014, is to date the largest German population study investigating widespread diseases. The DZL has been connected with the German National Cohort from the beginning through scientists from its own ranks and has in the meantime – since 2017 – established an associated partnership. In this cooperation, projects on the prevalence of lung health and lung diseases as well as other research projects are pursued.

The long-standing cooperation of DZL researchers with **PROGRESS (Pneumonia Research Network on Genetic Resistance and Susceptibility for the Evolution of Severe Sepsis)** was also formalized at the turn of the year 2016/17 with the admission of the network as an associated partner. Research is being conducted into the genetic basis for the pathogenesis of the disease and the resistance to community-acquired pneumonia. The research focus is on which factors influence whether pneumonia takes an uncomplicated or a severe course – including progression to septic shock.

Since 2015, an associated partnership has existed with the **Pulmonary Research Institute (PRI)** based at the LungenClinic Grosshansdorf. The PRI has at its disposal an extensive range of methods for studying functional changes and inflammatory processes in the lungs. Cohort projects in the field of COPD and bronchial asthma are conducted as well as phase I-IV clinical trials in the field of respiratory medicine with a focus on COPD, bronchial asthma, and rare diseases. The already long-standing close cooperation with the LungenClinic Grosshansdorf and the DZL has since been intensified through this new partnership.

The **Robert Koch Institute (RKI)** is the central institution of the German federal government in the field of application and action-oriented biomedical research. It has a unique population-based database for non-communicable as well as communicable lung diseases. An associated partnership with the RKI was agreed in March 2017. The expertise of the DZL could thus be significantly strengthened in the important field of epidemiology. The use of RKI-relevant data contributes to DZL research primarily in the areas of asthma and allergies, COPD, pneumonia and acute lung injury, and lung cancer. There is also collaboration in various pilot projects related to infectious diseases.

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

Asklepios Fachkliniken München-Gauting has been an integral part of lung research at the Munich site as an associated partner of the DZL since its inception. With 250 hospital beds, the Gauting clinics comprise one of the largest institutions in Germany specializing in lung diseases. Founded in 2008, the Asklepios biobank forms a close network with the biobanks of the other DZL sites in Giessen, Heidelberg, and the northern research con-

sortium. As of the beginning of 2020, the Asklepios Fachkliniken München-Gauting have been accepted as a member of the DZL.

Also with the beginning of 2020, the DZL was further strengthened by the establishment of the **Institute of Lung Health (ILH)** in Giessen. The joint funding by the ministries of the federal government (BMBF) and the state of Hesse (HMWK) under the umbrella of the DZL provides a valuable addition by establishing five new professorships and further working groups on the topics of vascular and parenchymal (pathological) changes and lung and heart interaction. An own research building financed by the state of Hesse is in preparation for construction.

Ever since the establishment of the DZL, the **German Respiratory Society (DGP)** has been an important strategic partner. Cooperation initiatives, among others in the area of promotion of young lung scientists and physicians as well as in the area of exchange with patient organizations, have been further strengthened. The DZL is regularly represented at the annual congresses of the DGP (see p. 38 and following). DZL board members and scientists have also held and still hold central positions in the DGP and thus contribute to the promotion of joint activities. For example, DZL board member Prof. Dr. Klaus F. Rabe (Grosshansdorf/Kiel) held the office of DGP President until March 2019.

The **Society for Pediatric Pneumology (GPP)** promotes research, networking and the exchange of scientists and clinicians as well as the dissemination of new findings in the field of pulmonary medicine in childhood and adolescence. Thus, the GPP is an important partner in the field of pediatric pneumology. The GPP regularly organizes scientific symposia and workshops that integrate DZL research content. DZL researchers also hold key positions in the GPP and are involved in the scientific working groups of the professional society. Thus, several DZL researchers are represented on the GPP board, ensuring a high level of exchange between the GPP and the DZL.

Since 2013, the DZL has been a full member of the **Technology, Methods, and Infrastructure for Networked Medical Research (TMF)**, the umbrella organization for networked medical research in Germany. The DZL cooperates closely with the TMF, particularly in the areas of biobanking and the establishment of a central data management. Especially in the field of biobanking, there is a regular and intensive exchange with the biobank and IT managers of the German Centers for Health Research and the German Biobank Node (GBN).

The DZL also supports various **anti-smoking campaigns**. One of these is the **Education against Tobacco (AGT)**, launched in 2012. In this initiative, more than 1,500 medical students from over 30 faculties in Germany, Austria and Switzerland volunteer each year to effectively educate more than 20,000 seventh-grade students about the dangers of tobacco smoking and to advocate for smoke-free classes in schools. In addition to students, instructors, physicians and professors are also involved in the project. The DZL chairman and other DZL researchers are members of the Scientific Advisory Board of the initiative. In 2014 and 2017, the initiative was awarded the **Federal Prize by the then German Chancellor within the framework of the „startsocial“ competition** for outstanding volunteer projects in Germany. This was followed in 2018 by the **EU Health Award** from the European Commission.

Together with the other **German Centers for Health Research (DZG)**, the DZL is part of a Germany-wide network in medical-translational research. The DZG benefit from the regular exchange of information on joint strategic, infrastructural and scientific topics at various work levels. For the benefit of patients, synergy effects can be

better utilized and created where, for example, topics in lung, cancer, infection or cardiovascular research overlap, as is the case in the disease areas of lung cancer, COPD, Pneumonia or Pulmonary Hypertension. Joint activities of the centers and key topics of the reporting year are described in more detail in the section on the DZG (see p. 44).

As one of the largest and most important societies in the field of respiratory medicine, the **European Respiratory Society (ERS)** is an important partner of the DZL. The close relationship is reflected, for example, in the appointment of Prof. Dr. Tobias Welte as president of the ERS for the 2018/19 term of office or the congress chairmanship in 2014 by DZL scientists at the ERS International Congress 2014 in Munich. The DZL is regularly represented with an information stand and presentations by DZL scientists at the annual congress of the European Respiratory Society (ERS). The ERS Congress is the largest gathering of respiratory researchers and clinicians in the world (see p. 33 and following).

DZL physicians are committed to finding optimal diagnostic and therapeutic approaches to lung disease by contributing to keeping **treatment guidelines** up to date. Medical guidelines aim to assist physicians in the treatment of their patients. They represent the current state of substantiated research findings and thus provide an important interface between science and medical practice.

In addition, there are numerous further strategic partnerships of the individual DZL sites with international partners from the fields of science and industry. For example, **Prof. Maria Belvisi** has strengthened the DZL's expertise in the area of industry contacts through her contribution as a member of the International Scientific Advisory Board. DZL scientists currently cooperate with well over 100 international partners from industry, primarily in basic and applied research projects and in clinical studies. These clinical studies, which are particularly focused on regulatory affairs, are conducted and supported by partners such as AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly and Company, GlaxoSmithKline, Hoffmann-La Roche or Novartis/ Novartis Pharmaceuticals.

DZL Academy: 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 organises 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), 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 2021

- ✅ Continuation of the digital lecture program
- ✅ Organization of the DZL Academy Symposium 2021 with about 180 participants
- ✅ Sponsoring of 60 DZL Academy Fellows to attend the European Respiratory Conference 2021
- ✅ Kick-start of the Mentoring Program 2022
- ✅ Organization of the Grant Writing Skills Course 2021
- ✅ Organization of joint DZG workshops in support of early career scientists, e.g. on the subject of „Epigenetic Techniques“ and „Lunch Time Career Talks“
- ↔️ Provision of mobility grant for scientific exchange between DZL sites – on hold due to the pandemic

Goals 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

First DZL Academy Symposium – Virtual exchange between early career lung researchers

From 29-30 September 2021, the DZL Academy hosted their first symposium entitled “When bugs hit the lung - infections as drivers of acute deterioration of lung disease”. About 180 early career scientists, experienced researchers and clinicians from different disciplines and organizations gathered virtually for an in-depth exchange on a hot topic of translational lung research.

The symposium was primarily aimed at early career scientists of the DZL Academy. However, members of other organizations such as the German Center for Infection Research (DZIF), the German Respiratory Society (Young DGP), the German Society of Infectious Diseases (DGI), and the German Society of Internal Medicine (DGIM) were also invited to the symposium, thus reflecting and contributing to the translational orientation of the symposium.

The program included 11 lectures on various aspects of lung infections, given by leading international experts in the field of chronic and acute lung diseases. In addition to the talks, the programme included a moderated discussion forum on electronic posters of 29 early career scientists. A two-hour virtual networking event in the evening of the first day enabled a personal exchange with senior scientists on topics such as career development and challenges and rewards of translational research.

The opening lecture was given by Prof. Dr. Tobias Welte, Director of the Clinic for Pneumology at the Hannover Medical School and Director of the DZL BREATH site, who talked about lessons learned from the current Corona pandemic. His talk was live-streamed to the DZIF Autumn School.

In the following five sessions, with two lectures each, the main topic “Infections of the lung” was examined from different perspectives. The speakers discussed mechanisms of acute lung injury caused by viruses and bacteria. They also talked about the influence of infections on disease progression in patients with pulmonary fibrosis, asthma or Chronic Obstructive Pulmonary Disease (COPD). Further talks focussed on the role of the lung microbiome and how air pollution (e.g. nanoparticles) may reactivate viruses and thus impact on chronic lung diseases.

The symposium was organized by the DZL Academy under scientific direction of Prof. Dr. Silke Meiners, group leader at the Research Center Borstel, Prof. Dr. Michael Kreuter, section head at the Thoraxklinik Heidelberg, Dr. Lucas Kimmig, assistant physician at the University Hospital Gießen and Dr. Espen Groth, assistant physician at the LungenClinic Grosshansdorf and member of the Young DGP.

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First DZL Grant Writing Skills Workshop for DZL-Academy Fellows

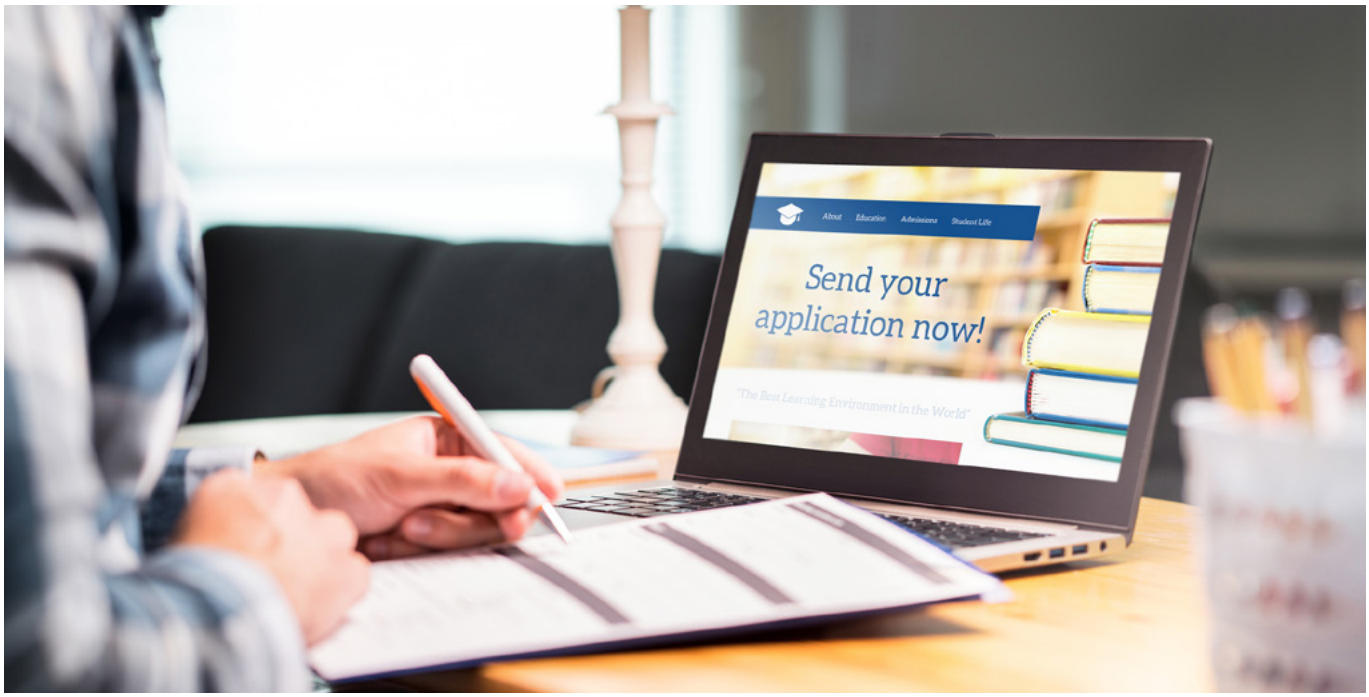
What makes a successful grant application? From 7-14 June 2021, 16 DZL Academy Fellows found answers to that question in the first virtual Grant Writing Skills Workshop, organised by the DZL. The early career researchers from five DZL-sites learnt through self-study with podcast-lectures, virtual live-lectures and group discussions how to draft convincing grant applications.

Scientific expertise and good ideas are not enough, when it comes to obtaining independent funding for your own research projects. It is at least as important that scientists know how to draft well written and convincing grant proposals. PhD students and postdocs usually have little experience in writing such applications and formal training can be an important stepping stone on the academic career path.

The 16 participants of the 2021 workshop were full of praise for content and format: “The course was absolutely amazing. The trainer was very knowledgeable and shared many invaluable tips and insights with us. She demonstrated the importance of looking at a grant not only from the applicant’s, but also from the reviewer’s perspective,” explains one participant. Another participant adds: “Being very unexperienced in writing grant proposals I now feel I understand what is asked of me to do so and I feel confident to try, as soon as the opportunity arises”.

A special feature of the course was the mix of self-study, live-online lectures and interactive group discussions. Prior to the course, participants had access to podcast-lectures which guided them step-by-step through the different sections of grant application forms and explained how to write an attractive CV on no more than two pages. “The podcasts were packed with information and will drastically change the way I write grant applications”, summarises one participant.

Based on the positive feedback of participants, the DZL is now offering regular virtual grant writing workshops for early career scientists. Interested DZL Academy Fellows can register for the course on the DZL Academy homepage. The workshop is targeted at advanced PhD students (at least in their third year of study) and postdoctoral researchers who are planning to apply for independent funding of their projects. Prior experience with writing grant applications is not a requirement for participating in the workshop.



Equal Opportunities and Diversity

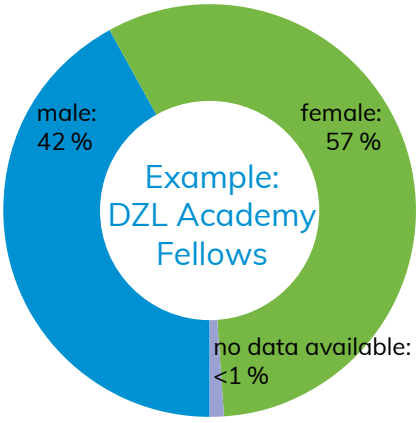
The German Center for Lung Research (DZL) and its member institutions are firmly committed to equal opportunities and equality at the respective DZL sites. For the DZL and its member institutions, it is a fundamental principle that no one should be excluded from a scientific career on the basis of gender, ethnic origin, nationality, age, or health status. After all, equal opportunities and equality pay off in several ways: They make it possible to fully exploit the existing potential for innovation and talent and to increase the quality of research thanks to diversely composed working groups.

In close cooperation with the corresponding committees at the respective DZL sites, we are therefore looking for talented individuals who can make the DZL even more diverse, innovative, and creative.

Concrete measures to ensure equality and equal opportunities between men and women, for example, include the gender equality programs of our member institutions. As part of these programs, female researchers are specifically recruited at every level, from trainee to scientific advisory board, in order to increase the proportion of female employees. In particular, the number of female DZL employees in management positions is to be increased. Since the DZL was founded in 2011, the proportion of female principal investigators (PIs) has increased from 14 % to around 24 %. The share of female employees in the total staff is 69 % in 2021. Read more about personnel and equality on p. 55.

Nationalities of the DZL Academy Fellows

Equal Opportunities and Diversity



The Public Face of the DZL

Compared to other widespread diseases, there is relatively low public awareness regarding lung disease, despite increasing disease numbers in the population. It is therefore particularly important that the DZL inform the general public, decision-makers, patients, and other target groups about lung disease and health.

The DZL's public relations activities currently include its own **scientific symposia** as well as its **presence at national and international congresses**, some of which were again held digitally in 2021, but others of which had to be postponed. In addition, the DZL offers **print** brochures, flyers, and annual reports, has a **website** (www.dzl.de), appearances in social media and conducts activities together with the **Lung Information Service**, for example in the context of events for patients. Since 2019, the magazine of the German Centers for Health Research (DZG) **SYNERGIE – Forschen für Gesundheit** has also been published twice a year.

As in previous years, the DZL also published current research results, event announcements, news about people at the center and other information regarding the DZL in the **news pages** of the journal Pneumologie, as was the case in May and December 2021.

Already in 2019 the DZL began to expand its public relations reach, starting with a **revised website**. With numerous news about DZL lung research and extensive information about the mission and structure of the DZL, the information offered on the DZL internet pages has been given a fresh, modern design. The website heading


Mitteilungen des DZL

Thieme

Mitteilungsseiten des Deutschen Zentrums für Lungenforschung

DZL Deutsches Zentrum für Lungenforschung

Klinische Studie des DZL

Norddeutsche Lungenkrebszentren bringen den HANSE-Lungen-Check auf den Weg

Im Frühsommer 2021 startete bei drei norddeutschen DZL-Partnern das bisher größte deutsche Programm zur Früherkennung von Lungen- und Herzkreislauferkrankungen. Frauen und Männer im Alter von 55–79 Jahren, die als (Ex-)Raucherinnern und Raucher ein erhöhtes Risiko für Lungentumore aufweisen, sind seither zum kostenlosen Lungencheck eingeladen. In einem mobilen Studien-Truck werden bis zu 5000 kostenlose Niedrigdosis-CT-Untersuchungen wechselnd zwischen der Medizinischen Hochschule Hannover, dem Universitätsklinikum Schleswig-Holstein (Campus Lübeck) und der LungenClinic Grosshansdorf angeboten. Eine Anmeldung ist unter https://www.hanse-lungencheck.de möglich.

Es ist wissenschaftlich erwiesen, dass Lungenkrebs-Screenings mittels Niedrigdosis-Computertomografie (CT) durch Erreichen einer früheren Erstdiagnose bei ehemaligen und aktiven starken Rauchern die Lungenkrebs-Sterblichkeit senkt. Bisher ist jedoch eine Früherkennung von Lungenkrebs in Deutschland noch nicht eingerichtet. Ein nationales Lungenkrebs-Screening-Programm, das von den gesetzlichen Krankenkassen übernommen würde, wird jedoch voraussichtlich nicht vor 2023 verwirklicht.

Der HANSE-Lungen-Check soll vor diesem Hintergrund als Pilotstudie den Nachweis erbringen, dass ein ganzheitliches und effektives Lungenkrebs-Früherkennungsprogramm in Deutschland durchgeführt werden kann. Daneben prüft ein breites wissenschaftliches Begleitprogramm verschiedene Möglichkeiten, um die Effektivität der Früherkennung von Lungenkrebs und anderen chronischen Erkrankungen zu verbessern. Die Studie wird vom Deutschen Zentrum für Lungenforschung (DZL) sowie vom Pharmakonzern AstraZeneca im Rahmen der Lung Ambition Alliance, einer Partnerschaft zwischen Industrie und Wissenschaft, unterstützt und gefördert. Wissenschaftlicher Leiter der Studie ist Prof. Dr. med. Jens Vogel-Claussen, leitender Oberarzt an der Medizinischen Hochschule Hannover.

Start des HANSE-Lungen-Checks im Juni 2021. (v. l. n. r.) Prof. J. Vogel-Claussen, wissenschaftlicher Leiter der Studie, Dr. S. Bohnet, Prof. M. Reck, Dr. B.-A. Bollmann, Prof. T. Welte, Dr. G. Schmid-Bindert und der erste Studienteilnehmer M. Scheele vor dem mobilen Studientruck. Foto: Karin Kaiser/MHH

Ausgewählte Preise und Auszeichnungen

Die beiden DZL-Direktoren **Prof. Klaus F. Rabe** (Standort ARCN) und **Prof. Tobias Welte** (Standort BREATH) erhielten den Ehrenpreis der Gesellschaft für Pädiatrische Pneumologie (GPP) für das Jahr 2020. Sie wurden damit für ihr berufspolitisches Engagement und ihren persönlichen Einsatz für eine engere Zusammenarbeit der pädiatrischen Fachgesellschaft mit der Deutschen Gesellschaft für Pneumologie und Beatmungsmedizin (DGP) ausgezeichnet. **Dr. Markus Weckmann** (Standort ARCN) erhielt den von der Deutschen Lungenstiftung gemeinsam mit der GPP vergebenen Johannes-Wenner-Preis 2020. Der mit 15000€ dotierte Preis ist für die Forschungs- und Projektarbeit bestimmt. Dadurch sollen Versorgung und Behandlung von Kindern mit Lungenerkrankungen verbessert werden.

Prof. Thomas Bahmer vom Standort ARCN erhielt den diesjährigen Preis für klinische Forschung der Deutschen Gesellschaft für Pneumologie und Beatmungsmedizin (DGP). Ein weiterer DGP-Forschungspreis ging an die DZL-Wissenschaftlerin **Dr. Karla Rubio** vom Max-Planck-Institut für Herz- und Lungenforschung (DZL-Standort UGMLC). Sie erhielt den DGP-Preis für die beste Grundlagenforschung 2020. Die Verleihungen der jeweils mit 10000€ dotierten Preise erfolgte im Rahmen des virtuellen DGP-Kongresses 2021.

Der DZL-Wissenschaftler **Dr. Ulrich Zißler** vom Standort CPC-M erhielt im September den „Joachim Ganzer Förderpreis für Allergen Immuntherapie" von der Deutschen Gesellschaft für Allergologie und klinische Immunologie (DGAKI). Der mit

"Publications" shows the latest publications by DZL scientists on a weekly basis. The **image film** of the research network has also been redesigned and can be viewed on the DZL website and on YouTube. Appearances in the social media channels (LinkedIn, Twitter) of the DZL and the DZL Academy round off the external image.

The comprehensive **DZL Annual Report 2020** was published in 2021, again in English and German versions. In addition to achievements and highlights of 2020, the report presented numerous accomplishments since the establishment of the DZL. In addition, various publications by and with DZL researchers appeared in professional journals and press articles.

Scientific Conferences and the DZL Annual Meeting

Usually, the DZL is represented at various congresses and symposia throughout the year. However, due to the Corona pandemic, most events had to switch to a scaled-down, digital format in 2021 again or even be cancelled. This was the case with the DGP Congress – the largest scientific forum in the field of pneumology in German-speaking countries, the ERS Congress – the annual meeting of the European Respiratory Society, and the annual meeting of the German Academic International Network (GAIN).

The most important and largest meeting, the DZL Annual Meeting, which is held alternately at all Center sites, had to be postponed to the following year in 2021 for the first time in DZL history due to the COVID 19 pandemic.

Focus on Patients

In its strategic orientation, the DZL increasingly focuses on the concerns and interests of patients. In this context, the **Lung Information Service (LIS)** has been a professional and reliable partner for direct and easy-to-understand information for patients since the foundation of the DZL. The scientists and physicians of the DZL sites assume an advisory role for the editorial contributions of the LIS and individual patient inquiries to the LIS. During the course of the year, the DZL and the LIS now organize several forums specifically for patients and family members, each with over 100 participants. However, in order to protect the particularly vulnerable groups of people, this in-person exchange was also dispensed with in 2021 (see p. 40 and following for more information on the LIS).

Dr. Pippa Powell, manager of the European Lung Foundation (ELF), makes an important contribution to strengthening the representation of patient interests in the DZL through her membership in the Scientific Advisory Board of the DZL. Since the founding of the European Respiratory Society (ERS), the ELF has pursued the goal of bringing together patients, the public and those working in the field to make a positive contribution to pneumology. One achievement resulting directly from this collaboration is the publication of the German translation of the **European Patient Ambassador Program (EPAP)**. The free online program is aimed at patients, family members and caregivers. With the aid of this program, they can develop their skills in obtaining information and dealing with medical staff, policy makers, researchers and the media. The program is suitable for patients with any condition. It was developed by the ELF and is now available in German, in addition to English, French, Italian and Dutch.

Since 2016, the DZL and the LIS have also been offering patients, family members, and the interested public an **overview of current clinical trials** conducted by DZL scientists. In the internet-based directory on the LIS web pages, the objectives, inclusion criteria, duration, and investigation or treatment methods of the respective study are presented in a generally understandable way. Interested patients can use the service to contact the study centers directly and thus gain easier access to clinical studies. The directory is continuously updated and regularly includes more than 100 different studies organized by disease.

This year, the DZL-funded HANSE study, which has been conducted at the ARCN (Lung Clinic Grosshansdorf and University Hospital Schleswig-Holstein, Lübeck Campus) and BREATH (Hannover Medical School) sites since June 2021, received special attention (see pp. 28-29). Germany's largest early detection program for lung cancer invites 12,000 test persons for a free lung check. Already in the first few months, quite a few cases of lung can-

Prof. Dr. Jens Vogel-Claussen, Patient Gerhard Lunow and Dr. Benjamin Bollmann (from left) at the follow-up examination

cer could be detected at an early stage and subsequently treated.

In the screening participant Gerhard Lunow, 72, lung cancer was detected at an early stage during the HANSE CT examination. The early diagnosis enabled effective treatment of the disease and prompted him to stop smoking.

The study is complemented by professional smoking cessation programs at the three study sites. The study's own website www.hanse-lungencheck.de provides all information, press releases and news about the HANSE study. The patron of the screening trial, Dr. Eckart von Hirschhausen, also provides information on the background to the trial in a YouTube video and offers insights into possible links of smoking to lung cancer.

Lung Information Service

The Lung Information Service (LIS), based at Helmholtz Munich, is an important professional and reliable partner of the German Center for Lung Research (DZL) for patient information. The LIS communicates scientifically sound, up-to-date and independent information gained directly from research to improve people's health and health literacy. In 2021, an average of 270,000 people per month obtained information from the LIS website, an increase of about ten percent over the previous year.

Information is provided via a comprehensive online portal, events for patients, and publications. At www.lungeninformationsdienst.de, the LIS provides basic knowledge as well as new research results in an understandable way. Key topics on the online portal of the Lung Information Service in 2021 included: Pneumonia, Vaccination, Lung Research, or Imaging. The need for assured health information on current topics was particularly evident in 2021 for the topic of RS virus (RSV), in addition to the continued high interest in questions about COVID-19. The background for this was: due to the less restrictive Corona measures, infections rose again in 2021 as more children were exposed to the virus. In November

and December 2021 alone, the Lung Information Service base text on RSV tracked over 333,000 individual page views.

In cooperation with the DZL, the internet-based study platform with information on clinical studies was further expanded. By the end of 2021, more than 140 studies had been recorded in the platform.

In November 2021, the LIS offered an online seminar entitled “Preventing allergies and asthma – prevention begins before birth”. More than 130 participants informed themselves about the current state of knowledge.

Media interest in topics covered by the Lung Information Service also remained high – in 2021, articles appeared in online portals with a wide reach, such as T-Online or Allergo News, as well as in radio and print media, such as Südwestdeutscher Rundfunk or Pharmazeutische Zeitung, among others.

In 2021, the LIS published four articles in the journal “Patientenbibliothek – Atemwege und Lunge” (Patient Library – Airways and Lung) (circulation 30,000) in its own section “Lungenforschung aktuell” (Current Lung Research). In these articles, DZL scientists also provide expert statements. In 2021, these were Dr. Ali Önder Yildirim (CPC-M), Dr. Herbert Schiller (CPC-M), Prof. Dr. Tobias Welte (BREATH) and Prof. Dr. Klaus F. Rabe (ARCN) on new therapeutic approaches and antibodies in COPD, on the ‘Human Cell Atlas’ and on community-acquired pneumonia (CAP).

The monthly newsletter now reaches more than 4,300 subscribers. The Lung Information Service is also active in social media. It has its own Facebook page with more than 4,700 subscribers and publishes news from research several times a week via the news service Twitter.

In addition to knowledge transfer, the year 2021 at the Lung Information Service was all about dialog: On the occasion of the 10th anniversary of the Lung Information Service, Helmholtz Munich invited participants to a digital round table with the guiding question “Knowledge for better health – How do we achieve even more together?”. Guests included Prof. Dr. Werner Seeger, Chairman of the Board of Directors of the German Center for Lung Research, and other renowned guests from politics, science and medicine. Klaus Holetschek, Bavarian Minister of State for Health and Care, as well as site directors and coordinators of the German Center for Lung Research sent greetings on the occasion of the anniversary.

Selected DZL Highlights of 2021

Study Examines Benefit of Pulmonary Hypertension Medication for Idiopathic Fibrosis

Patients with severe Idiopathic Pulmonary Fibrosis (IPF) often develop additional Pulmonary Hypertension (WHO classification PH group 3) or, at least, are at an increased risk for it. An international, multicenter, double-blind, randomized, and placebo-controlled clinical trial investigated whether treatment with Sildenafil (approved for PH), when administered in addition to the Pulmonary Fibrosis medication pirfenidone, is effective. The findings have recently been published in the medical journal *Lancet Respiratory Medicine* (Behr et al., 2021).

How healthy lungs develop in children

DZL researchers have studied the composition of the lung flora in infants and young children with and without Cystic Fibrosis (CF) and found out how a healthy lower respiratory microbiome develops. The study was published in the renowned journal *npj Biofilms and Microbiomes* (Pust et al., 2020).

Monocyte count allows prognosis on disease progression in patients with Idiopathic Pulmonary Fibrosis

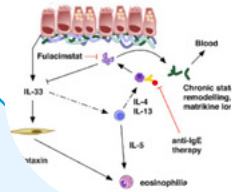
A simple blood count to determine the number of a subset of white blood cells — the monocytes — might allow predictions on disease progression of patients with Idiopathic Pulmonary Fibrosis (IPF) and help physicians and patients to plan therapeutic steps. This is the result of a study among 2,067 patients conducted by TLRC scientists in an international collaboration recently published in the *American Journal of Respiratory and Critical Care Medicine* (Kreuter et al., 2021).

Review paper about successes of donor lung preservation published

DZL scientists report the success of ex vivo lung perfusion as an established procedure for donor lung preservation in a review published in the *American Journal of Transplantation* (Iske et al., 2021).

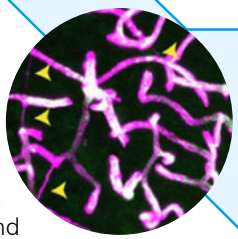
Strong antiviral immunity in the upper airways protects children from severe COVID-19

Children are also infected with the new SARS-CoV-2 coronavirus but have a very low risk of getting severely ill with COVID-19 compared to adults. In a study published in the scientific journal *Nature Biotechnology*, DZL scientists were able to show that the child's immune system is much more active in the upper respiratory tract than in adults and thus better equipped to fight the virus.



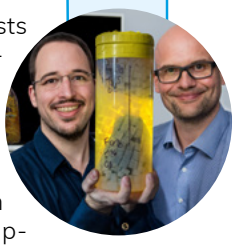
Will an individual asthma therapy succeed? – Lung collagen degradation might tell
Researchers of DZL shed some light on the various types of asthma: they analyzed lung collagen degradation and found a way to predict the course of an antibody therapy with omalizumab. The results have been published this month in the *European Respiratory Journal.* (Weckmann et al., 2021).

Improved lung function with Itepekimab in COPD
Could the anti-IL-33 monoclonal antibody ittepekimab be a treatment option for moderate to severe Chronic Obstructive Pulmonary Disease (COPD)? That's what researchers investigated in a study of the antibody's efficacy, safety, and tolerability. The results were published in the journal *The Lancet Respiratory Medicine.* (Rabe et al., 2021).



Mechanism deciphered: How the coronavirus damages blood vessels in the brain
SARS-CoV-2 affects not only the lungs and airways but also influences many human body organs. How it damages small blood vessels in the brain was deciphered by a consortium of the German Centers for Lung Research (DZL), Infection Research (DZIF), and Cardiovascular Research (DZHK). They published their results last week in *Nature Neuroscience*. Prof. Dr. Peter König of DZL site ARCN accounted for electron microscopy (Wenzel et al., 2021).

New X-ray technique reveals vascular damage in intact COVID-19 lung for the first time
An international research team led by DZL scientists Prof. Dr. Danny Jonigk and Willi Wagner demonstrated changes in blood vessels caused by infection with SARS-CoV-2. Using a highly innovative X-ray technique, they were able to show that massive remodeling of the finest blood vessels occurs in severe COVID-19. They published the technical procedure in *Nature Methods* (Walsh et al., 2021) and the clinical application in the *American Journal of Respiratory and Critical Care Medicine* (Ackermann et al., 2021).



Tumor DNA in blood provides early indication of lung cancer progression
DZL scientists have developed a detection method for tumor DNA. In a study published in the journal *npj Precision Oncology*, they show how the detection of this tumor-specific DNA in the blood of many patients can detect the development of resistance even earlier than was previously possible with imaging methods (Angeles et al., 2021).

The German Centers for Health Research

The main aim of the federal government's health research program is to be able to combat widespread diseases more effectively. With the establishment of the German Centers for Health Research (DZG), the federal and state governments have created the prerequisites for this. The German Centers for Health Research are long-term, equal partnerships between non-university research institutions such as the Max Planck, Fraunhofer, Helmholtz and Leibniz Institutes, and universities with university hospitals. The DZL is one of six DZG centers established between 2009 and 2012 at the initiative of the German Federal Ministry of Education and Research. They share existing expertise and thus make a significant contribution to closing knowledge gaps and improving prevention, diagnosis and therapy of common disease patterns. The centers are dedicated to the following diseases: Cancer (DKTK), Diabetes (DZD), Cardiovascular Diseases (DZHK), Infectious Diseases (DZIF), Lung Diseases (DZL), and Neurodegenerative Diseases (DZNE). Two additional centers for child and adolescent health and for mental health are in the process of being established.

The strategic collaboration of leading researchers in the DZG strengthens Germany's position as a center of science in international competition and significantly increases its attractiveness for young scientists in Germany and abroad. The bundling of different disciplines and competencies has already led to a significantly increased international visibility of translational, clinical application-oriented research in Germany.

The six centers in the DZG have worked closely together from the start to exchange knowledge and expertise and implement synergies. The DZG forums (four meetings in 2021) focus on the strategic development and cooperation of the DZG centers. In the past few years, the cross-DZG cooperation has been further expanded and exchanges have been established in working groups on topics including biobanking, artificial intelligence, data management, promotion of young talent, public relations, prevention, global health, and regulatory aspects of clinical studies (stakeholder ability). At the end of 2020, a strategy paper was adopted for the future collaboration of the DZG centers and for the use of funding.

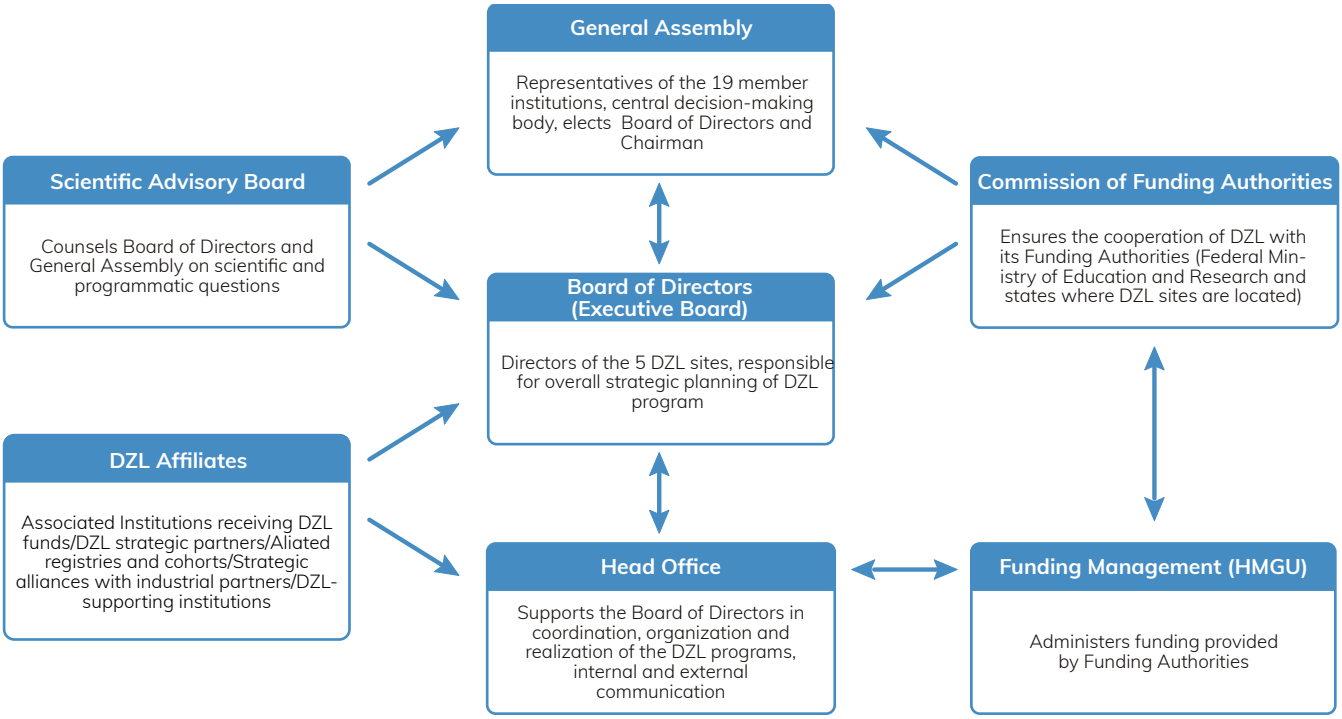
DZG

DEUTSCHE ZENTREN DER GESUNDHEITSFORSCHUNG

In 2021, several successful events – in online formats due to the pandemic – were organized as part of the DZG's joint promotion of young scientists. These included, for example, an online workshop on "Epigenetic Techniques", an online seminar series on "Translating Science into Clinical Practice", as well as offerings from the "DZG Lunch Time Career Talks" series. These interactive talks are designed for graduate students and postdoctoral fellows who want to learn more about potential career paths for scientists. DZL Academy Fellows get the opportunity to meet scientists who have taken different career paths. Thus, they learn what it is like to be a Medical Scientist, Head of a Core Facility, Clinical Scientist, Scientific Author, Scientist in Industry, Employee in a Government Agency, Science Communicator or Science Manager. Lectures are held regularly every three months.

Two more issues of the joint DZG SYNERGIE magazine were also published in 2021. The joint success was reflected in the awarding of the magazine in the fall of 2021 with the "Berliner Type" silver prize. The "Berliner Type" competition honors the best print products from Germany, Austria, and Switzerland. With the award, the jury honored the expressive design of the SYNERGIE magazine, which shows with intense color, with precision and vividness, the diversity and depth of the research topics with which the DZG are working to combat the major widespread diseases of cancer, diabetes, cardiovascular, infectious, pulmonary, and neurodegenerative diseases.

DZL Organization



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

DZL Executive Board

- Prof. Dr. Werner Seeger (DZL chairman and speaker) – Director of the DZL site Giessen, Marburg, Bad Nauheim (Universities of Giessen and Marburg Lung Center, UGMLC)
- Prof. Dr. Hans-Ulrich Kauczor – Director of the DZL site Heidelberg (Translational Lung Research Center, TLRC)
- Prof. Dr. Klaus F. Rabe – Director of the DZL site Borstel, Grosshansdorf, Kiel, 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)

DZL Head Office

- Dr. Christian Kalberlah, Managing Director
- Susanne Klasen, Management Assistant
- Christin Krakau, Management Assistant
- Natalie Liebel, Management Assistant
- Rogin Honar, Management Assistant (since February 2022)
- Alina Zidaric, Press and Public Relations (on parental leave until August 2022)

Scientific Advisory Board

The Scientific Advisory Board of the DZL is made up of internationally acclaimed experts in lung research. In 2021 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 – Finance Department (Commercial Funding Management, Helmholtz Zentrum München)

General Assembly

The DZL currently has 19 member institutions. In addition, the DZL has ten associated partners (as of 2021).

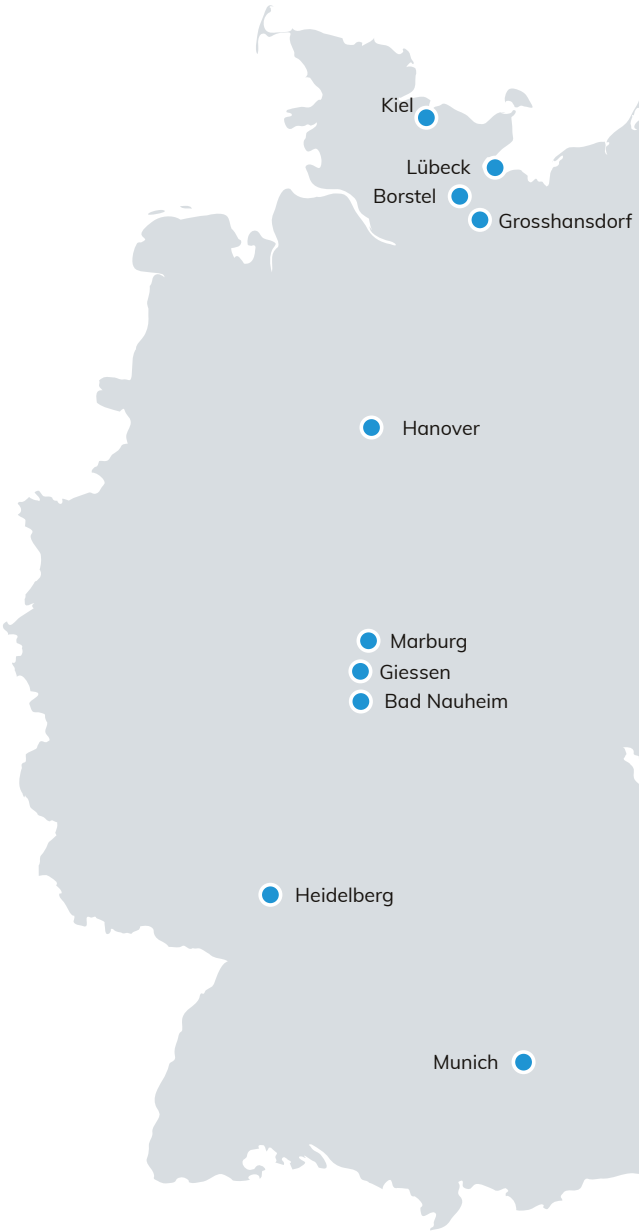
Commission of the Funding Authorities

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

Selected Prizes and Awards 2021

Name and DZL Site	Prize / Award
Prof. Dr. Thomas Bahmer Kiel	Research Award of the German Respiratory Society (DGP) for the best scientific paper in the field of basic research
Prof. Dr. Dr. Friedrich Grimminger **Prof. Dr. Werner Seeger** Giessen	Medal of Honor of the Faculty of Medicine of Justus Liebig University Giessen
Prof. Dr. Dr. Friedrich Grimminger Giessen	Von Behring Roentgen Research Medal for Lifetime Achievement
Prof. Dr. Uwe Haberkorn Heidelberg	Among the most cited scientists worldwide
Verena Häfner Munich	Postdoc Fellowship of the European Society for Immunodeficiencies
Prof. Dr. Michael Kreuter Heidelberg	European Respiratory Society (ERS) Teaching Award
Dr. Mareike Lehmann Munich	Rising Star Award
Michal Mastalerz Munich	Young Investigator Merit Award of the Research Training Group 'Targets in Toxicology' (LMU Munich)
Dr. Carmela Morrone Munich	German Dissertation Award Pneumology of the German Lung Foundation
Prof. Dr. Ana Pardo-Saganta Giessen	Young Investigator Award AstraZeneca Foundation
Prof. Dr. Klaus Rabe Grosshansdorf **Prof. Dr. Tobias Welte** Hanover	Honorary Award of the Society for Pediatric Pneumology (GPP) for the year 2020
Prof. Dr. Didier Stainier Bad Nauheim	Funding from the European Research Council (ERC)
Dr. Ulrich Zißler Munich	Joachim Ganzer Award for Allergen Immunotherapy of the German Society for Allergology and Clinical Immunology (DGAKI)
DZG-Magazin SYNERGIE	Berliner Type Award in Silver

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

- German Cancer Research Center
- European Molecular Biology Laboratory
- Heidelberg University
- Thorax Clinic at Heidelberg University Hospital
- Heidelberg University Hospital

Munich

Comprehensive Pneumology Center Munich (CPC-M)
Site Director: Prof. Dr. Dr. 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

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. 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
Scientists and clinicians of the Airway Research Center North (ARCN) focus on research in the areas of Chronic Obstructive Pulmonary Disease (COPD) and Lung Cancer as well as Asthma and Allergy. This translational research consortium combines top-level expertise in basic research and medicine in the field of pulmonology in Schleswig-Holstein. As the largest North German clinic specializing in lung and airway diseases with more than 12,000 patients treated per year, the LungenClinic Grosshansdorf, together with the University Hospital Schleswig-Holstein (UKSH) and the Medical Clinic Borstel, is responsible for the clinical and patient-centered research at the ARCN. The Research Center Borstel focuses on the study of infectious and non-infectious lung diseases and contributes to the success of the ARCN in basic research and the development of animal models. Additional partners include researchers at the University of Lübeck and Kiel University, who are focused on the study of asthma in animal models, the analysis of the epigenetic causes of lung diseases, and on the development of novel imaging techniques. Cohort projects and clinical studies are conducted together with the Pulmonary Research Institute at the LungenClinic Grosshansdorf. To strengthen the synergy between clinical and basic research, the BioMaterialBank Nord (BMB Nord) has been established as a joint central infrastructure. In the area of asthma, our physicians specialized in pediatric and adult lung medicine work closely together for a better understanding of different disease courses. This crosslink between complementary partners at the ARCN aims to support the collaborative implementation of translational research strategies.

DZL Site Hanover
Biomedical Research in Endstage and Obstructive Lung Disease (BREATH)

Partner Institutions of the Site
- Hannover Medical School (MHH)
- Fraunhofer Institute for Toxicology and Experimental Medicine (ITEM), Hanover
- Leibniz University Hanover (LUH)
- CAPNETZ Foundation

Prof. Dr. Tobias Welte

- Director of the Hanover DZL site BREATH
- Head of the Department of Respiratory Medicine of Hannover Medical School
- Board Member and Treasurer of the Biomed Alliance since 2020
- 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 Forum of International Respiratory Societies (FIRS) 2019
- 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
- Speaker of the DFG review board “Inflammation” since 2012
- 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 endstage 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
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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 TLRC DZL site
- Provisional Director of the Department of Translational Pulmonology at Heidelberg University Hospital
- Medical Director of the Department of Diagnostic and Interventional Radiology at Heidelberg University Hospital

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Research Profile
The Heidelberg Translational Lung Research Center (TLRC) is an interdisciplinary center for translational lung research, where physicians and scientists at Heidelberg University Hospital and the Medical Faculty of Heidelberg University, the Thoraxklinik at Heidelberg University Hospital, one of Germany's oldest and largest hospitals specializing in lung disease, and the non-university research centers (the German Center for Cancer Research and the European Molecular Biology Laboratory) all work together to combat lung disease. The common goal is to improve diagnosis and therapy of chronic lung diseases in children and adults by promoting the close collaboration and exchange of expertise between basic research and clinical research. 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 and Allergy (AA), Pneumonia and 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
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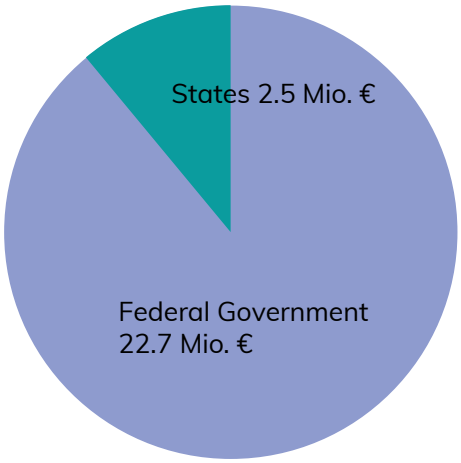
Research Profile
Translational research at the Universities of Giessen and Marburg Lung Center (UGMLC) focuses on lung diseases caused by inflammatory and hyperproliferative processes. This includes research on the impact of environmental factors on the development of Asthma and Chronic Obstructive Pulmonary 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.

Finance and Personnel

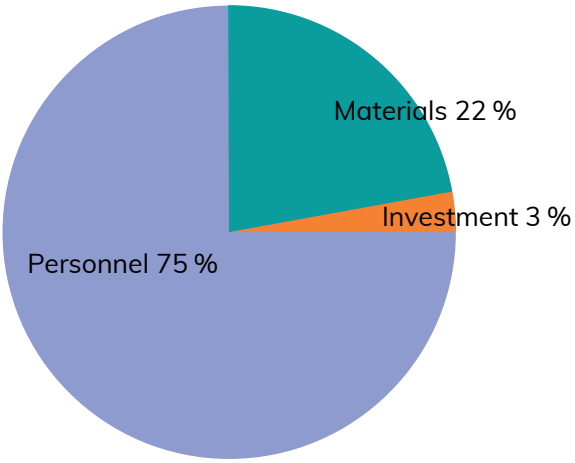
Total Funding and Cost Breakdown 2021

The total funding for the DZL in 2021 was 25.2 million Euros. 90 % was received from the German Ministry of Education and Research (BMBF) and 10 % from the German states with participating DZL centers. Across the eight Disease Areas studied by DZL scientists, around 50 major research projects were supported. Finance is managed by the DZL Funding Management based at the Helmholtz Center in Munich. The Funding Management forwards the project funds to the DZL partner institutions. With the general DZL funding and additional direct funding to the Justus Liebig University Giessen, the state of Hessen Ministry provided 2.2 million Euro funds for establishment of the Institute for Lung Health (ILH) at the Giessen partner site (as of April 2022).

Total Funding 2021



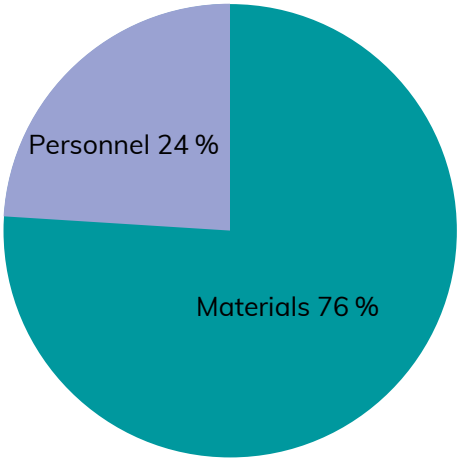
Cost Breakdown: DZL Expenses 2021

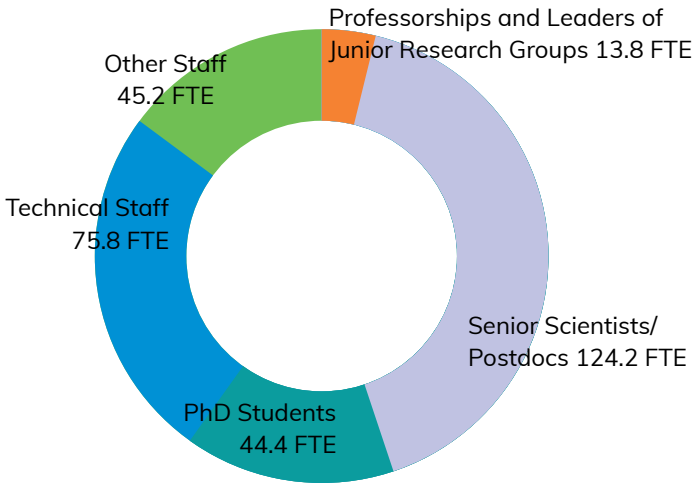


Cost Breakdown: DZL Expenses 2021

The DZL e. V. is financed through membership fees collected from each member institution as well as from donations. Membership fees amounted to € 635.500 in 2021. The 2021 Annual Financial Statement and Year-End Close of the DZL was prepared by the firm Haas & Haas (Giessen).

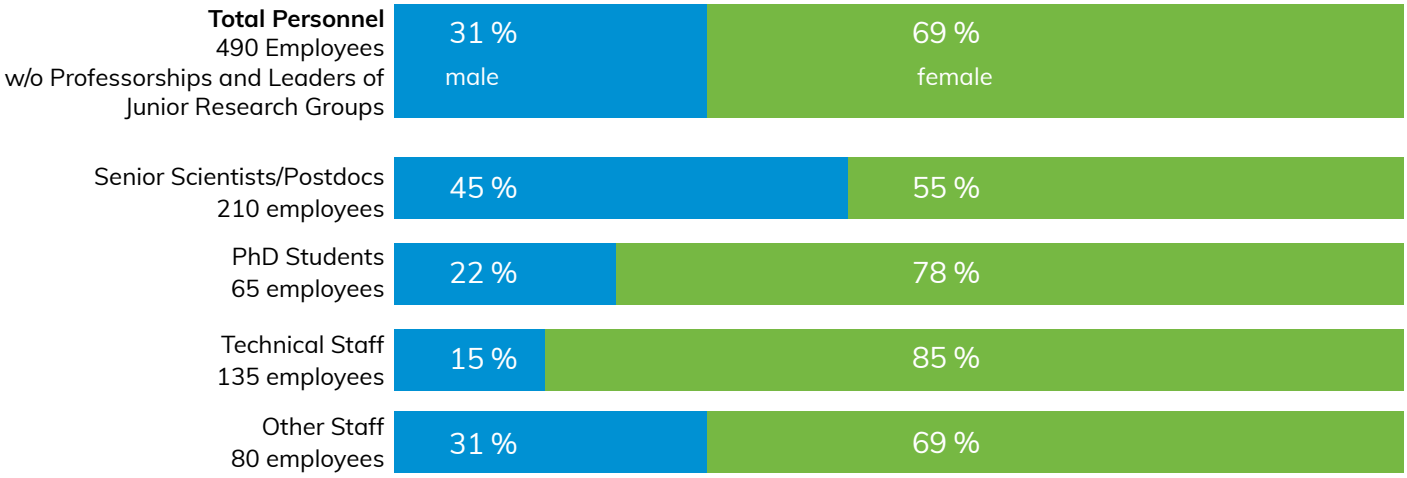
Cost Breakdown: DZL e. V. Expenses 2021





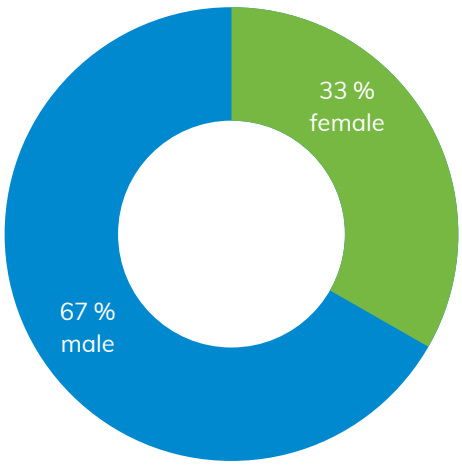
Personnel and Gender Equality 2021

In 2021, employment relationships with 511 persons (303.4 full-time equivalents, FTE) at the five partner centers and associated partner institutions were funded with DZL money. Of these individuals, 343 were women (67 % of the total personnel).

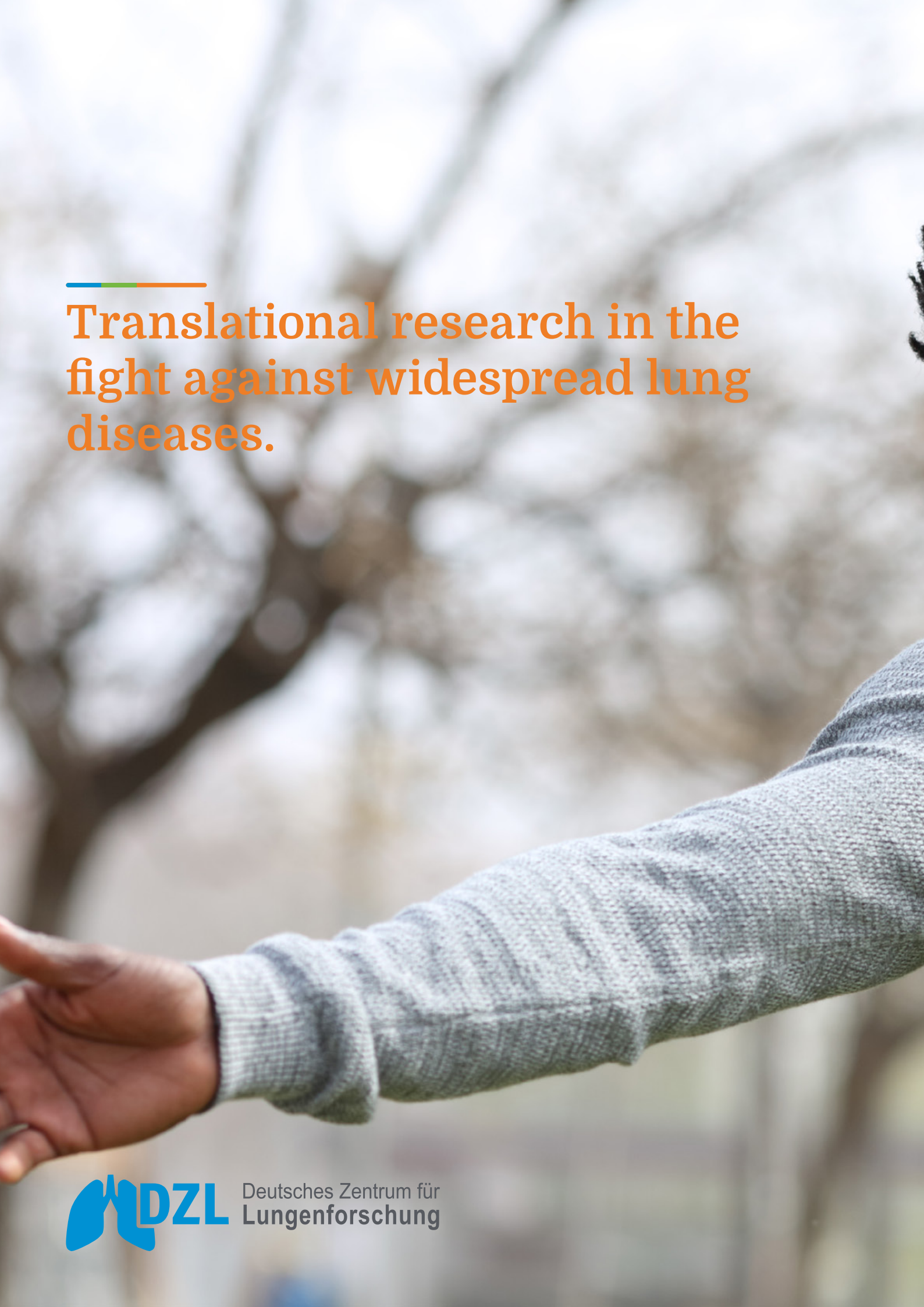


Professorships and Leaders of Junior Research Groups 2021

In 2021, 21 professorships and leaders of junior research groups were funded within the DZL, 7 of whom are women (33 %).



Translational research in the fight against widespread lung diseases.



DZL Deutsches Zentrum für Lungenforschung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Glossary

AA	Asthma and Allergies
AGT	Education against Tobacco
ALI	Pneumonia & Acute Lung Injury
ARCN	Airway Research Center North
BIH	Berlin Institute of Health
BMBF	German 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
COMPERA	Prospective Registry of Newly Initiated Therapies for Pumonary Hypertension
COPD	Chronic Obstructive Pulmonary Disease
COSYCONET	German COPD and Systemic consequences - Comorbidities NETwork
CPC-M	Comprehensive Pneumology Center-Munich
DGAKI	German Society for Asthma and Clinical Immunology
DGI	German Society for Infectiology
DGIM	German Society of Internal 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
ECFS	Scientific Advisory Board
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
GAIN	German Academic International Network
GPP	Society for Pediatric Pneumology e.V.
ILH	Institute for Lung Health
IPF	Idiopathic Pulmonary Fibrosis
ITEM	Fraunhofer Institute for Toxicology and Experimental Medicine
LC	Lung Cancer
LIS	Lung Information Service
NAKO	German National Cohort
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)
SAB	Scientific Advisory Board
TLRC	Commission of Funding Authorities
TMF	Technology, Methods, and Infrastructure for Networked Medical Research
UGMLC	Universities of Giessen and Marburg Lung Center

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