Deutsches Zentrum für Lungenforschung

DZG DEUTSCHE ZENTREN DER GESUNDHEITSFORSCHUNG

Annual Report 2020

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Foreword

The COVID 19 pandemic, which in 2020 also reached Germany, has drastically shown us that a life in good health is anything but a certainty. Everyone has experienced slowdowns and even standstills due to the imposed restrictions in both the public and private spheres. At times, feelings of powerlessness arose when clinicians at our center cared for the sick. It is not only individuals somewhere outside our daily field of vision who have been and continue to be affected, but all of us worldwide, including our families, friends and acquaintances.

Yet by acting together with solidarity and professionalism, we experienced how we can take decisive and effective measures against the pandemic. It is success stories such as the impressively rapid development of an effective and safe vaccine made in Germany that also give us the drive and inspiration to meet our scientific and clinical responsibility to help people suffering from lung diseases. These achievements include numerous studies that DZL researchers have initiated after only a short lead time on the clinical picture of COVID-19-induced lung failure, as well as the opening of the Institute for Lung Health (ILH) at the DZL site in Giessen, where the scientists and clinicians involved have been devoting themselves to acute inflammatory and chronic disease processes in lung diseases and researching repair and regeneration mechanisms to restore lung health. Across Germany, our researchers have worked on current issues in pulmonary medicine and have, among other things, gained new insights into a possible diagnosis via breath analysis ("breathomics", p. 7), explored a promising therapeutic approach to cure COPD (p. 9) or described the healthy development of the airway microbiome in young children (p. 11). Promising active substances for inhibiting infections with coronaviruses (p. 13) were investigated, as was the impressive regenerative capacity of the alveoli (p. 15). Our researchers were able to refine the diagnosis of idiopathic pulmonary hypertension (p. 17) and further understand the damage to the lung caused by microthrombi after a SARS-CoV-2 infection (p. 19), as well as the "complicity" of a lung tumor with its surrounding tissue (p. 21). They report on the establishment of a high-quality biomaterial collection of lung tissue samples (p. 23), show how they plan to combat lung cancer through individualized early detection (p. 26), and have observed brush cells eliminate respiratory pathogens (p. 25).

We invite you to explore this overview of the exciting research being pursued every day by the many colleagues at our center in the fight against widespread lung diseases. We wish you fascinating reading!

Prof. Dr. Werner Seeger
Chairman of the Board and Speaker

Prof. Dr. Hans-Ulrich Kauczor
Board Member

Prof. Dr. Klaus Rabe
Board Member

Prof. Dr. Erika v. Mutius
Board Member

Prof. Dr. Tobias Welte
Board Member

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

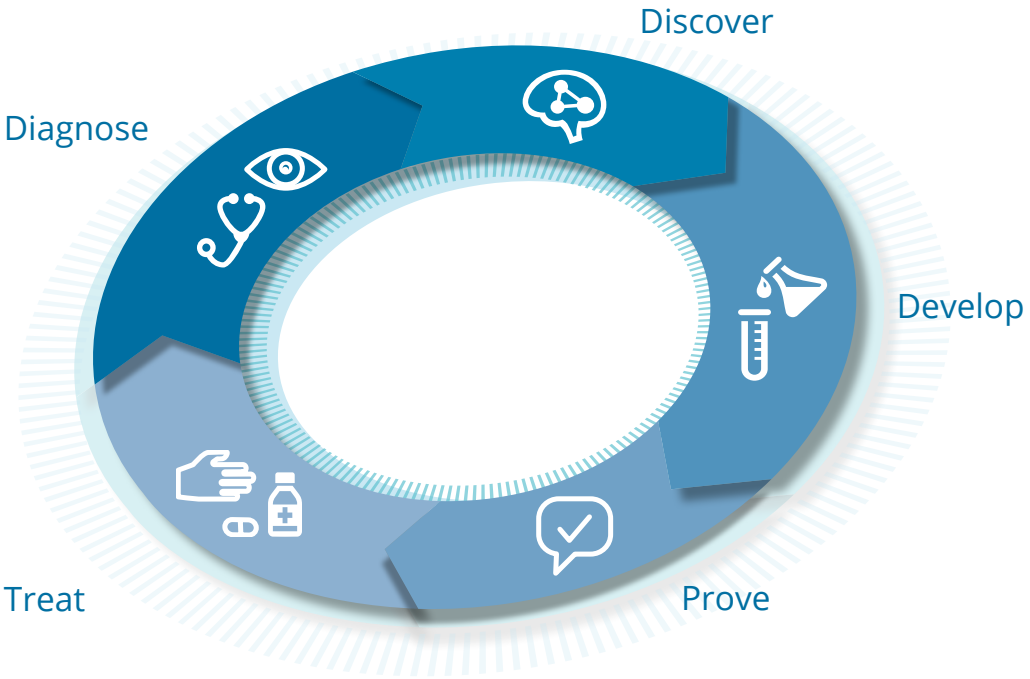
The Board of the German Center for Lung Research

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 250 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 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 2020

- ✓ 10 joint publications of several DZL sites (achieved: 20)
- ✓ 450 additional medical consultations in the ALLIANCE asthma cohort
- ✓ 15 ongoing projects on the use of biomaterial and accompanying data
- ✓ Description of microbiome in animal models

Goals 2021

- 15 joint publications of several DZL locations
- 450 more medical consultations in the ALLIANCE cohort
- Recording of Corona infections in the ALLIANCE cohort
- 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

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One breath of air for asthma diagnosis – is that possible?

What do exhaled substances tell about someone's health status? This is a question that also DZL scientists are posing. They published results on asthma diagnosis through breath analysis in the *European Respiratory Journal*. The results were disappointing, but the conclusions are important.

The patient exhales into a tube, the clinical lab analyzes substances contained therein, the physician makes the diagnosis. Such a process would be advantageous: the risk of complications inherent to blood drawing or surgical removal of tissue for diagnostic purposes would be reduced. This is one of the reasons why 'breathomics' has become very popular recently. The relatively new research area deals with exhaled volatile organic compounds (VOCs). The crucial question: is it possible at all to tell just from breath, if someone is ill or healthy? And how can we determine this? Detection methods range from non-technical solutions – such as cancer-sniffing dogs – to electronic noses which allow for live analysis of substance patterns. These experiments are based on the assumption that particularly lung diseases have an impact on breath composition.

Results initially disappointing – the response nevertheless great

The DZL research team investigated the extent to which VOCs from exhaled air are suitable for distinguishing between different forms of asthma in 133 adult patients of the ALLIANCE cohort. The disappointing result: no substance was found whose value was statistically valid. The authors have now published these results in the *European Respiratory Journal*. Although isolated differences were found in older studies, the DZL researchers caution that breath analysis for asthma – and other diseases – is still far from clinical application. First, methodological issues would have to be clarified and results from individual research groups externally validated. Dr. Olaf Holz from Fraunhofer-ITEM in Hanover is the first author of the study and has been concerned with the topic for a long time: "Although we report 'negative results' here, the response to our paper is great. The question of whether the measurement of exhaled VOCs is ready for everyday clinical use is a topic of intense interest in the community." Another possible reason for the results: Suitable biomarkers in exhaled air simply do not exist for asthma. Only further experiments can clarify whether

this is actually the case. Scientists of the DZL sites ARCN (LungenClinic Grosshansdorf, University Medical Center Schleswig-Holstein and Pulmonary Research Institute), BREATH (Fraunhofer-ITEM and Medical School Hannover) and CPC-M (Clinic of the Ludwig-Maximilians-Universität Munich) collaborated in this study.

The DZL is conducting another study on exhaled breath analysis (without looking at VOCs): In EMoLung, researchers intend to predict the course of a lung cancer disease by studying ribonucleic acids. An established biomarker of exhaled breath is nitric oxide (NO) which indicates inflammation. As its chemical nature is inorganic, NO is not considered a VOC.

Further Information

Holz O, Waschki B, Watz H, Kirsten A, Abdo M, Pedersen F, Weckmann M, Fuchs O, Dittrich A-M, Hansen G, Kopp MV, v. Mutius E, Rabe KF, Hohlfeld JM, Bahmer T (2020) Breath volatile organic compounds and inflammatory markers in adult asthma patients – negative results from the ALLIANCE cohort. Eur Respir J 57(2):2002127

Chronic Obstructive Pulmonary Disease (COPD)

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

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

Goals Achieved in 2020

- ↔ 20 joint publications of several DZL sites (18 publications)
- ✓ Video conference calls every two months for research coordination
- ✓ Joint project with the population-based Hamburg City Health Study to study risk factors (such as COPD) in COVID-19 (500 patients)
- ✓ Identification of comorbidity clusters in COSYCONET through AI
- ✓ Long-term study of COSYCONET patients regarding the dimension of lung change and identification of progression parameters

Goals 2021

- 20 joint publications by several DZL locations
- Continued long-term study of COSYCONET patients
- Influence of e-cigarette smoke on the respiratory tract of the fruit fly
- Comparison of the lung microbiome of smokers, ex-smokers and never-smokers
- Identification of the immune proteasome as a biomarker and therapeutic target structure

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Promising approach to treat COPD

DZL scientists at Helmholtz Zentrum München and the German Cancer Research Center (DKFZ) have succeeded in curing COPD in mice exposed to chronic cigarette smoke. They published their results in the journal *Nature*. The research group's goal is to test the new approach in the next few years in first clinical trials in humans.

Despite intensive research, it has not yet been possible to cure COPD. Current treatments attempt to alleviate symptoms. "One of the biggest problems with COPD is that the lungs cannot regenerate themselves," said Dr. Ali Önder Yildirim, director and head of the research group Immunopathology of COPD at Helmholtz Zentrum München and principal investigator of the study. "Therefore, a treatment that can actually cure the disease must restore damaged lung tissue and stop the cell death of lung epithelial cells."

In 2009, a DKFZ research group led by Prof. Dr. Mathias Heikenwälder succeeded in preventing chronic inflammation and fibrosis in the liver. To this end, the scientist blocked the lymphotoxin beta receptor signaling pathway. There are many parallels between the liver and the lungs in the development of diseases: As in chronic liver inflammation, immune cells in COPD form newly organized structures called tertiary follicles that are relevant to disease progression. They can only form when the lymphotoxin beta receptor is activated in the lungs – the same receptor that Heikenwälder had already blocked in his study on the liver. "Our goal was to find out what the functions of this receptor and its signaling pathways are in COPD and whether we can use them for therapeutic purposes," Yildirim said. The researchers therefore blocked the signaling pathways of the lymphotoxin beta receptor in the lungs of mice that had developed COPD-typical symptoms (immune cell follicles, fibrosis and death of lung epithelial cells) due to chronic exposure to cigarette smoke.

The result: blocking prevented the formation of immune cell follicles in the lungs of COPD mice and suppressed the cell death of lung epithelial cells. Surprisingly, the signaling blockade stimulated lung tissue to regenerate on its own. "Even though the mice were exposed to cigarette smoke, we observed complete recovery of lung tissue," said Dr. Thomas M. Conlon from Yildirim's Munich research group. "In addition, we saw that as the lungs healed, there was also improvement in secondary diseases such as muscle atrophy."

Furthermore, the researchers found that lung tissue regeneration is stimulated by so-called Wnt signaling in damaged lung epithelial cells. "We see our study as a new therapeutic approach. Our idea is to develop a lymphotoxin beta receptor blocker to reduce lung epithelial cell death and inflammation. This then simultaneously releases Wnt signals that could stimulate lung tissue regeneration," Yildirim said.

In initial preclinical experiments, the research group already demonstrated that lymphotoxin beta receptor signals in human lung tissue samples behave identically to those in mice. The results, published in the journal *Nature*, have significant potential to improve regenerative lung medicine. The goal is to test the new therapeutic approach in human clinical trials in the coming years.

Further Information

Conlon TM, John-Schuster G, Heide D, Pfister D, Lehmann M, Hu Y, Ertüz Z, Lopez MA, Ansari M, Strunz M, Mayr C, Angelidis I, Ciminieri C, Costa R, Kohlhepp MS, Guillot A, Günes G, Jeridi A, Funk MC, Beroshvili G, Prokosch S, Hetzer J, Verleden SE, Alsafadi H, Lindner M, Burgstaller G, Becker L, Irmler M, Dudek M, Janzen J, Goffin E, Gosens R, Knolle P, Pirotte B, Stoeger T, Beckers J, Wagner D, Singh I, Theis FJ, de Angelis MH, O'Connor T, Tacke F, Boutros M, Dejardin E, Eickelberg O, Schiller HB, Königshoff M, Heikenwalder M, Yildirim AÖ (2020) Inhibition of LTβR signalling activates WNT-induced regeneration in lung.
Nature 588(7836):151-156

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 2500 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 2020

- ✅ Investigation of the T cell receptor repertoire and methylome of peripheral blood cells from monozygotic twins with CF
- ✅ Comparison of the development of the respiratory microbiome in healthy and children with CF in the first years of life
- ✅ Comparison of organoids and *in vivo* biomarkers of CFTR function to determine therapeutic effects of CFTR modulators
- ✅ Investigate the effects of lumacaftor-ivacaftor on changes in lung structure and function, and the airway microbiome in F508del homozygous patients with CF
- ✅ Investigate the role of the ubiquitin ligase NEDD4.2 in the pathogenesis of mucociliary dysfunction

Goals 2021

- Complete and evaluate first efficacy and safety study of CFTR modulators lumacaftor-ivacaftor in F508del homozygous infants
- Complete and evaluate CFTR biomarker study to investigate the attenuation of the basic CF defect using triple therapy
- Establishment of the sweat secretion assay as novel CFTR biomarker
- Establishment of rheology to test efficacy of novel therapies on viscoelastic properties of CF mucus
- Evaluation of the efficacy of cell therapy by pulmonary transfer of host defense cells 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

How the lung microbiome develops in healthy children and children with cystic fibrosis

On average, a human being consists of about 30 trillion body cells - and just as many bacteria. Without them, we are not viable. The lungs also have a microbiome, a community of bacteria, viruses and fungi that is essential for the organ to function. DZL researchers have studied the composition of the lung flora in infants and young children with and without cystic fibrosis and discovered how the microbiome of the lower respiratory tract develops.

Until a few years ago, the human lower respiratory tract was considered sterile. Therefore, most studies examined the microbiology of the lungs only in acute infections or chronic lung diseases. In our work, we collected cough swabs from healthy children aged three weeks to six years for the first time, tested them for the microorganisms present and compared them with those from cystic fibrosis patients of the same age. One methodological challenge was the requirement to elucidate microbial community composition from hundreds of bacteria, fungi, and viruses with high sensitivity and specificity from a sample containing 5-20 nanograms of microbial DNA without contaminating samples and solutions with microbes from the environment during processing. Another challenge was to establish a metagenome pipeline to quantitatively determine the population and network structure and metabolic potential of the respiratory metagenome via high-throughput sequencing on Illumina or Nanopore substrates.

To their surprise, the scientists found that the lung microbiomes of the healthy and sick children hardly differed from each other during the first three years of life. They had a very similar composition of apathogenic and commensal pathogens, which are interrelated and form a kind of network. This includes the pathogens typical of cystic fibrosis, such as *Staphylococcus aureus* or *Pseudomonas aeruginosa*. In the first year of life, this network is somewhat more unstable in children with cystic fibrosis, but there is hardly any difference in two- to three-year-olds. It is not until the next three years that the microbiome changes again in children with cystic fibrosis. From elementary school age, the diversity of bacterial species decreases again. Disease germs predominate and chronically settle in the lungs. The sensitive network of apathogenic and commensal pathogens breaks down. In healthy children, on the other hand, the network remains stable, although their lungs have a significantly higher bacterial load. The rare bacterial species are just as important as the dominant pathogens. For example, when the microbial network is massively disrupted, it is primarily the rare pathogens that stabilize the network and protect the human host from developing harmful dysbiosis. In other words, the overall composition of the microbiome is critical for lung health.

This study was the first to generate data on the respiratory metagenome of healthy infants, which can be used as a comparative cohort for other studies in the future. The study also provides a crucial insight for the treatment of cystic fibrosis: While the lung microbiome of older patients with cystic fibrosis can no longer be transformed into a healthy microbial network with current symptomatic therapy, there is a window of opportunity in young children to influence the lung holobiome favorably (for example with CFTR modulators) for further disease progression.

Further Information

Pust MM et al (2020) The human respiratory tract microbial community structures in healthy and cystic fibrosis infants. NPJ Biofilms Microbiomes 6:61

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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 2020

- ✅ Identification and molecular characterization of macrophage-associated repair factors (e.g. Plet-1) for therapeutic use in severe viral pneumonia
- ↔️ Translation of the basic scientific and preclinical findings on the antiviral effects of inhaled liposomal cyclosporine A (CsA) against MERS-CoV and SARS-CoV-2 in a pilot study for the treatment of patients with early symptomatic COVID-19 disease (L-CsA-I-COVID)
- ✅ Establishment of a clinical study (first patient in 2020) to prevent progression of COVID-19 progression to ARDS by administering the growth factor GM-CSF (GI-COVID) by inhalation

Goals 2021

- Inhaled liposomal cyclosporine A (CsA) against SARS-CoV-2, pilot study in early symptomatic COVID-19 disease (L-CsA-I-COVID)
- Pathomechanisms of macrophage depletion and reprogramming in severe viral pneumonia to define new therapeutic target structures
- Development of further human-relevant infection models in the context of COVID-19 as well as for precise disease modeling
- Implementation of the ESsCOVID study (NCT04576728, use of trimodulin in severe COVID-19 disease, phase IIa)

Cyclophilin inhibitors against infections with the coronavirus?

Middle East respiratory syndrome coronavirus (MERS-CoV) emerged in Saudi Arabia in 2012, causing severe pneumonia with up to 35 % mortality. To date, there is no specific treatment or vaccine available.

In the present study, molecular mechanisms of inhibition of MERS-CoV by the cyclophilin inhibitors cyclosprin A (CsA) and alisporivir (ALV), a non-immunosuppressive CsA derivative, were investigated and their suitability as curative agents against MERS-CoV infection was evaluated.

In cell culture experiments with primary human alveolar epithelial cells infected with MERS-CoV, a reduction in pathogen concentration and viral replication was observed after administration of both inhibitors, CsA and ALV.

Regarding the molecular mechanism, CsA was shown to upregulate interferon regulatory factor 1 (IRF1), resulting in a pronounced type III interferon (IFN-lambda) response and expression of antiviral genes. In turn, downregulation of these factors led to increased viral replication despite the presence of CsA.

Comparative studies in animal models with oral administration of CsA confirmed these results: CsA resulted in reduced viral replication and is associated with increased levels of IFN-lambda and improved outcome. These data are confirmed in translational and preclinical SARS-CoV-2 models.

In summary, CsA efficiently inhibits coronavirus replication *in vitro* and *in vivo*, through activation of inflammatory antiviral cellular defenses, particularly through IFN-lambda. Therefore, CsA is a suitable candidate for the treatment of MERS-CoV and SARS-CoV-2 infections, and a clinical trial is currently being planned.

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Further Information

Sauerhering L, Kupke A, Meier L, Dietzel E, Hoppe J, Gruber AD, Gattenloehner S, Witte B, Fink L, Hofmann N, Zimmermann T, Goesmann A, Nist A, Stiewe T, Becker S, Herold S, Peteranderl C (2020) Cyclophilin inhibitors restrict Middle East respiratory syndrome coronavirus via interferon-λ in vitro and in mice. Eur Respir J Nov 26;56(5):1901826

Diffuse Parenchymal Lung Disease (DPLD)

Diffuse parenchymal lung disease (DPLD) comprises more than 200 different lung diseases, most with severe courses. Although remarkably different in origin, natural course, and genetic background, all DPLDs ultimately involve progressive scarring, extensive lung remodeling, and impaired cellular interaction and composition. In some forms of DPLD, the underlying cause is understood and may be either genetic or environmental. In other forms of DPLD, such as in the idiopathic interstitial pneumonia group, the underlying causes are not fully understood and new therapies are urgently needed. To date, only a few drugs have been approved for the treatment of pulmonary fibrosis. While these "antifibrotics" are able to slow the progression of scarring, they cannot completely halt or even reverse the disease. Furthermore, there is no complementary or causative treatment option, so lung transplantation is still the only curative treatment approach. To better understand the pathogenesis of these diseases and to develop better treatment options, internationally renowned basic scientists and clinicians are collaborating across sites in the DPLD disease area of the DZL. This collaboration serves to better understand disease pathogenesis and develop treatment options. The use of highly specialized techniques and the development of the latest artificial intelligence methods are just as important here as the continuous further development of clinically significant *in vitro* and *in vivo* models.

Goals Achieved in 2020

- ☑ Characterization of the alternative macrophage activation, inflammasome and programmed cell removal in the DPLD taking environmental influences into account
- ☑ Characterization of the epithelial-mesenchymal crosstalk with a focus on the epithelial-cellular plasticity in neonatal and adult DPLD
- ☑ Establishment of (pre-)clinical studies to evaluate new diagnostic tools in fibrosis (single cell analysis, biomarkers) taking comorbidities into account
- ☑ Utilization of experimental disease models including stem cell organoids using second hits

Goals 2021

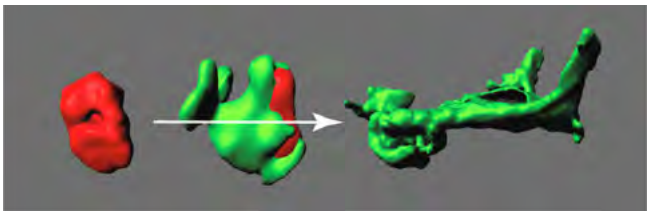
- Elucidation of the role of non-coding RNAs and the architecture of the cell nucleus in the epithelial-mesenchymal transition in lung cancer and pulmonary fibrosis
- Collection of real-world data to influence the natural course of lung function and survival through antifibrotic therapies
- Description of the role of magnetic resonance imaging in imaging bronchopulmonary dysplasia
- Characterization of the role of the Wnt signaling pathway in the development of senescence in the alveolar epithelium

How Pulmonary Alveoli Regenerate

When the lungs regenerate after an illness or environmental-related diseases, there are a number of cell differentiation processes whose molecular details have not yet been fully understood. Researchers of the DZL site Munich (CPC-M) and the ICB (Helmholtz Center Munich) have discovered a new stem cell state and have been able to decode cellular hierarchy during alveolar regeneration following injury. The findings of their work have been published in *Nature Communications*.

Lung diseases account for one-sixth of deaths worldwide. Due to its surface, the lung epithelium is particularly susceptible to microbial and environmentally caused damage. Various stem cell populations can repair this damage by replacing the damaged cells. In the process of cell differentiation, stem cells change their gene activities and hence, in the long term, also their identity. The molecular control and dynamics of such processes have scarcely been investigated so far. Using time-resolved single-cell transcriptomics and lineage tracing, the team of Herbert Schiller (CPC-M) and Fabian Theis (ICB) has now been able to partially decode cellular hierarchy during alveolar regeneration (pulmonary alveoli) following injury.

Together with their colleagues, scientists of the Institutes for Lung Biology and Disease as well as Computational Biology analyzed the course of cell differentiation processes for 28 different types of cells and compiled a map with single-cell RNA sequencing data of cell state changes during lung regeneration. Here, they found that in pulmonary fibrosis, a particular transitional state is abnormally regulated. This fault in the course of the regeneration process might possibly be the cause for developing the disease. These findings provide a significant molecular basis for developing future therapies.



During lung regeneration, alveolar stem cells (red) change their shape and turn into flat al-veolar epithelial cells (green).

“In order to reprogram cells in the pathologically modified lung back to ‘normal’, we must first gain an understanding of the process and control of cell state change in the course of normal recovery. Our data suggest that certain regenerative stem cell states in the scarred lungs of patients with pulmonary fibrosis persist chronically,” said Dr. Herbert Schiller, head of the study.

Further studies to unveil the exact mechanism of the newly discovered stem cell state in the pathogenesis of fibrosis are already underway.

Further Information

Strunz M, Simon LM, Ansari M, Kathiriya JJ, Angelidis I, Mayr CH, Tsidiridis G, Lange M, Mattner LF, Yee M, Ogar P, Sengupta A, Kukhtevich I, Schneider R, Zhao Z, Voss C, Stoeger T, Neumann JHL, Hilgendorff A, Behr J, O‘Reilly M, Lehmann M, Burgstaller G, Konigshoff M, Chapman HA, Theis FJ, Schiller HB (2020) Alveolar regeneration through a Krt8+ transitional stem cell state that persists in human lung fibrosis. Nat Commun Jul 16;11(1):3559

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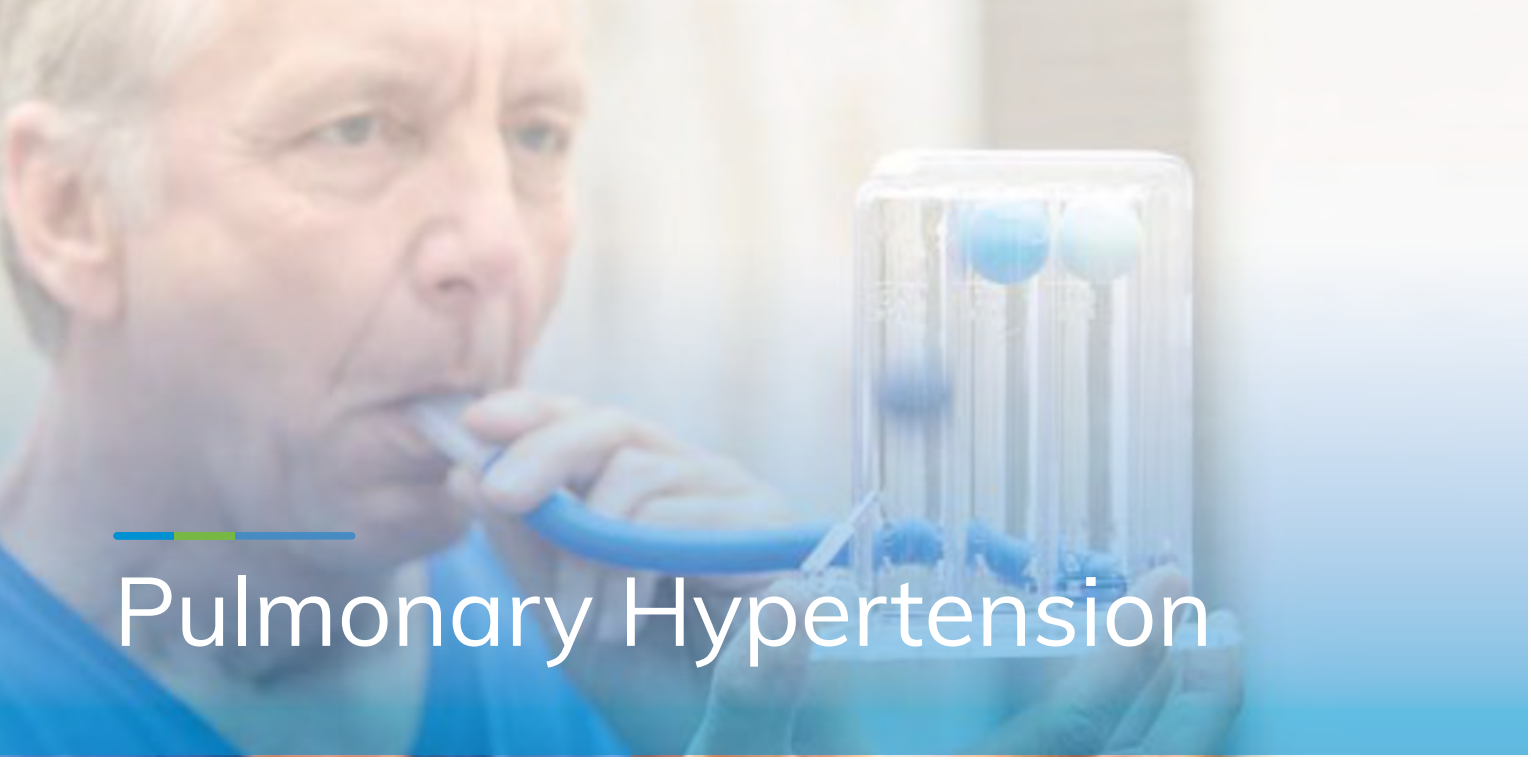

Pulmonary Hypertension

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 2020

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

Goals 2021

- Epigenetic studies of vascular cells in pulmonary hypertension
- 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
- Conduct of preclinical experiments to test anti-proliferative substances in pulmonary hypertension
- Evaluation of databases to validate new risk-adjusted therapy strategies

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Idiopathic Pulmonary Hypertension – cluster analysis based on the COMPERA registry reveals different phenotypes

The COMPERA registry (Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; www.COMPERA.org), established in 2007, is an ongoing web-based PH registry that collects baseline, follow-up, and outcome data from patients who receive targeted therapies for PH. Specialized centers from European countries contribute to this data collection, with 80 % of the enrolled patients coming from Germany, among them patients from DZL centers in Hanover, Giessen, Heidelberg, and Munich. Based on the COMPERA data, a selected cohort of patients diagnosed with Idiopathic Pulmonary Arterial Hypertension (IPAH) was subjected to cluster analysis. IPAH is a form of PAH where the cause/s is/are unknown and all forms of PAH (e.g. PAH associated with connective tissue or liver disease, HIV infection) have been excluded. All forms of PAH show the same vascular pathologies and share a common therapeutic approach. Nevertheless, there is considerable variability in the clinical presentation of these patients. Cluster analysis in this study was based on baseline characteristics, survival, and response to therapy (changes from baseline in functional class (WHO FC I-IV), 6 min walking distance, cardiac biomarkers, and risk-stratification). Within the selected IPAH cohort (n=846) we identified three distinct clusters: Cluster 1: 76 % female patients, median age 45 years, no co-morbidities, mostly never smokers, mostly normal lung function (normal DLCO). Cluster 2: 98 % female patients, median age 75 years, frequent co-morbidities, 94 % show at least one risk factor for left heart disease, non-smokers, mostly normal lung function (normal DLCO). Cluster 3: 72 % male patients, median age 72 years, frequent co-morbidities (risk factors for left heart disease), smoking history (79 %), 53 % with reduced lung diffusion capacity (low DLCO). Cluster 1 is the smallest subgroup (n=106) and can be described as “classical IPAH”: mostly younger female patients without cardiac risk factors. Cluster 2 (n=306) consists of older women who have no smoking history but multiple other risk factors for (left) heart disease. The largest group (Cluster 3, n=434) are older, mostly male patients with a smoking history and multiple cardiac risk factors. The response to therapy was the most positive in Cluster 1: 5-year survival was 84.6 % in Cluster 1, 59.2 % in Cluster 2, 42.2 % in Cluster 3. It is likely that the differences between the clusters are not only based on the different age structures but also on different pathogenetic mechanisms (e.g. smoking), which may also apply to the therapy response. In conclusion, based on the data analysis, despite the “uniform” diagnosis of “IPAH,” there are substantial differences in the general condition, response to therapy, and survival of patients.

Further Information

Hoeper MM, Pausch C, Grünig E, Klose H, Staehler G, Huscher D, Pittrow D, Olsson KM, Vizza CD, Gall H, Benjamin N, Distler O, Opitz C, Gibbs JSR, Delcroix M, Ghofrani HA, Rosenkranz S, Ewert R, Kaemmerer H, Lange TJ, Kabitz HJ, Skowasch D, Skride A, Jureviciene E, Paleviciute E, Miliauskas S, Claussen M, Behr J, Milger K, Halank M, Wilkens H, Wirtz H, Pfeuffer-Jovic E, Harbaum L, Scholtz W, Dumitrescu D, Bruch L, Coghlan G, Neurohr C, Tsangaris I, Gorenflo M, Scelsi L, Vonk-Noordegraaf A, Ulrich S, Held M (2020) Idiopathic pulmonary arterial hypertension phenotypes determined by cluster analysis from the COMPERA registry. J Heart Lung Transplant 39(12):1435-1444

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 2020

- ☑ *Ex-vivo* lung perfusion for immune modulation in the context of allogeneic lung transplantation
- ☑ ECMO therapy for COVID-19
- ☑ Psychosocial assessment and its predictive validity in the context of lung transplantation
- ☑ Histopathological analysis of COVID-19 lungs to identify the pathogenesis
- ☑ Cross-site projects for xenotransplantation of the lungs

Goals 2021

- First *in vivo* analyses of the biohybrid lung in an animal model
- Studies on innovative prophylaxis, diagnostics, therapy and prognosis of CLAD
- Establishing the *ex vivo* setting for xenotransplantation
- Optimizing 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

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How the Coronavirus damages the lungs

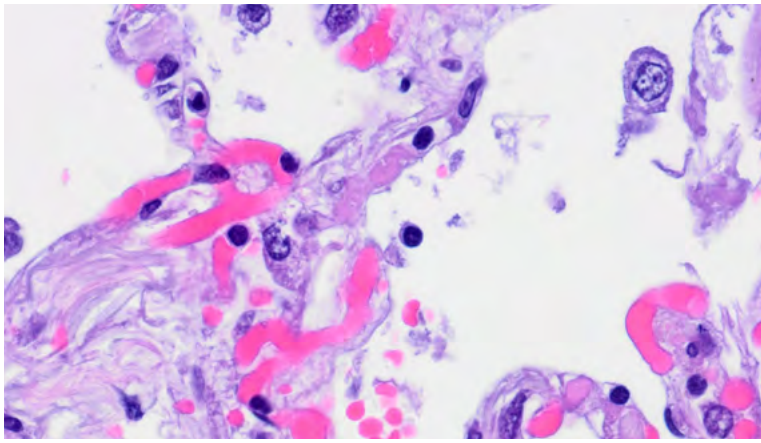
Like severe influenza, infection with the Coronavirus can cause massive damage to the respiratory tract and lead to fatal lung failure. However, exactly which molecular changes SARS-CoV-2 triggers in the lung tissue of patients and how these differ from the damage caused by the influenza virus is to date poorly understood. In order to better understand the disease processes, an international research team from Germany, the U.S., Belgium and Switzerland, led by Prof. Dr. Danny Jonigk, a lung specialist at the Institute of Pathology at Hannover Medical School (MHH), has now examined lungs from patients who died from COVID-19 and compared them with those from patients who died of influenza.

"The study improves our understanding of why lung function is so severely impaired in SARS-CoV-2 infected people with severe disease processes," said Professor Jonigk, who is affiliated with the German Center for Lung Research (DZL). The renowned *New England Journal* of Medicine has now published the findings of the study entitled "Pulmonary Vascular Endothelialtis, Thrombosis and Angiogenesis in COVID-19".

Microthrombi clog the finest vessels

"For the first time, we examined the tissue samples synergistically with a very wide range of methods from micro-computed tomography, 3D electron microscopes and various molecular biological methods in order to track down the pathways of SARS-CoV-2," Jonigk said.

The scientists were initially able to demonstrate the already known acute damage pattern in the lungs of COVID-19 patients, the so-called diffuse alveolar damage. This occurs when the walls of the alveoli become inflamed and covered by protein deposits, making it more difficult for the oxygen to diffuse into the blood. "We also found a massive number of blood clots in all sections of the blood vessels in the lungs, but especially in the finest vessels, the capillaries," the pathologist said. "These microthrombi clog the fine pulmonary vessels and thus increase the patient's shortness of breath."



Microthrombi in the small blood vessels of the lung in COVID-19 infection

The phenomenon also exists in severely damaged lungs after influenza infections, but the number of these small blockages is much lower in people who have died from flu.

Particularly noticeable is a finding that doctors usually only know from tumor diseases, autoimmune diseases or scarring processes: SARS-CoV-2 apparently triggers a special form of new blood vessel formation in the lungs.

"This so-called intussusceptive neo-angiogenesis has not yet been described in the context of diffuse alveolar damage and fundamentally distinguishes COVID-19 from similarly severe lung infections caused by influenza viruses," Jonigk said.

"In summary, the three changes within the lungs in SARS-CoV-2 infections described in detail for the first time in our study are massive blood vessel damage, excessive blood coagulation with clogging of the finest pulmonary vessels and the formation of new blood vessels that is characteristic of COVID-19." The pathologist sees the results of the study as a further piece in the puzzle of deciphering COVID-19, but noted that the mystery of the Coronavirus is far from being solved. Further studies are needed to understand the mechanisms of the vascular changes and ultimately to translate them into therapeutic approaches.

Further Information

Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, Vanstapel A, Werlein C, Stark H, Tzankov, A, Li WW, Li VW, Mentzer SJ, Jonigk D (2020) Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. N Engl J Med 383(2):120-128

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 2020

- ✓ Publication on immunological microenvironment of wild-type and oncogene-driven tumors
- ✓ Demonstration of tumor inhibition by targeted suppression of alveolar macrophages
- ✓ Demonstration that lymphocyte subpopulations promote tumor progression and metastasis
- ✓ Publication on the impact of B lymphocytes and tumor-infiltrating lymphocytes in predicting the benefit of immunotherapy in NSCLC
- ✓ Highly significant prediction of therapy response by measuring specific biomarker combination immediately after the start of chemotherapy

Goals 2021

- Generation of new preclinical models to study the impact of immunotherapy treatment on the tumor microenvironment
- Obtaining new insights into the contribution of different subsets of macrophages, fibrocytes and T cells to tumor growth and metastasis
- Identification of new biomarkers and therapy goals that are geared towards reprogramming the metabolic tumor adaptation
- Identification, preclinical characterization and longitudinal tracking of new molecular risk factors in oncogene-driven NSCLC
- Investigation of the influence of p53 mutations on therapy resistance

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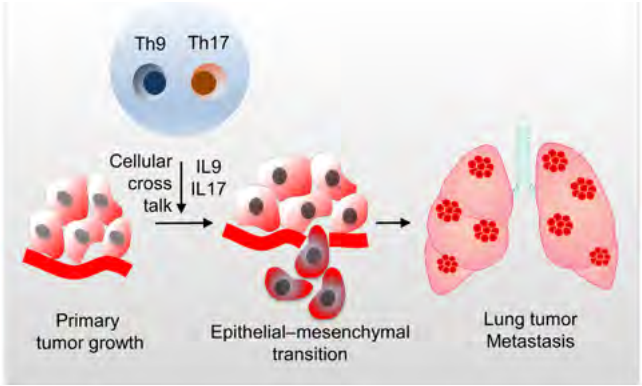
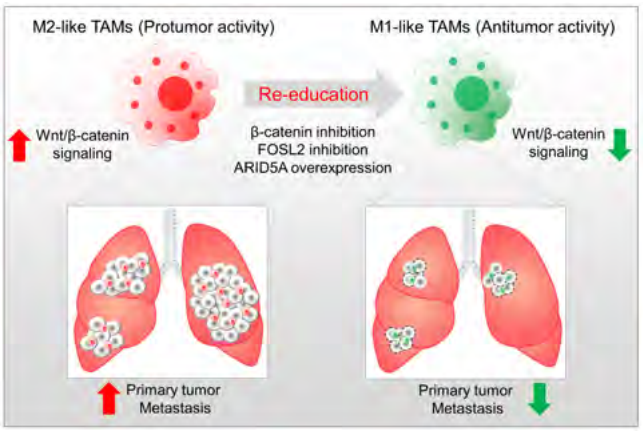
The Tumor Microenvironment: accomplice in tumor progression

Immunotherapies offer a relatively new perspective in lung cancer therapy. Unfortunately, only a subset of tumors responds to currently available therapies. To identify new targeted therapies, Professor Rajkumar Savai´s research team at the Max Planck Institute for Heart and Lung Research in Bad Nauheim (MPI) and the Justus Liebig University Giessen (JLU), analyzed the entire spectrum of cells in the tumor microenvironment (TME). The TME is a key player in tumor growth and metastasis. A high density of tumor-associated macrophages (TAMs) correlates with a poor prognosis in the lung cancer and a reduced overall patient survival. TAMs can be distinguished into tumor-inhibiting M1-like and tumor-promoting M2-like subtypes. How M1 TAMs transform to cells that promote the tumor was the subject of research. A molecular switch mediated by the protein β-catenin has been shown to play a central role in this process. Targeted suppression of this protein and its downstream signaling pathways that control the reprogramming of tumor-inhibiting into tumor-promoting TAMs reactivates the lung antitumor immunity. This approach could thus offer a novel treatment strategy in lung cancer both in combination with traditional therapeutics



IL-9- and IL-17-producing T cells promote lung tumor cell mobility and thus metastasis.

or with immunomodulatory drugs. An important additional component of the TME is immune cells. The immune system as first line of defense against pathogens serves also as immune surveillance. It identifies and eliminates degenerated cells, thus preventing the development of a tumor. However, it has been shown that lymphocytes can aid tumor cells to escape immune control and thus also promote proliferation. Certain subpopulations of lymphocytes, particularly Th9 and Th17 lymphocytes, have been



Reprogramming of tumor-promoting macrophages into tumor-inhibiting macrophages.

linked to carcinogenesis, but the mechanisms involved have not yet been elucidated. Epithelial-mesenchymal transition (EMT) is a key process in which initially epithelial cells give rise to mobile cells that circulate in the bloodstream and subsequently form metastases elsewhere. In a series of experiments the researchers have now demonstrated that the exchange between tumor immune cells and lung cancer cells can promote tumor progression and metastasis in particular. In cell culture experiments, activated lymphocytes stimulated lung tumor cells to convert into the mesenchymal cell type and thus promoted cell division and migration. This was accompanied by elevated levels of the cytokines IL-9 (Interleukin-9) and IL-17. Greater numbers of Th-9 and Th-17 lymphocytes in patient lung cancer tissue negatively correlate with overall survival. Experiments in the animal model confirmed these results. Targeted inhibition of the cytokines IL-9 and IL-17 using neutralizing antibodies was found to decrease EMT and significantly reduced lung cancer progression and metastasis. Antibody treatment against IL-9 and IL-17 could thus represent a novel immunomodulatory therapeutic concept in lung cancer.

Further Information

Salazar et al (2020) Microenvironmental Th9 and Th17 lymphocytes induce metastatic spreading in lung cancer. J Clin Invest 130(7): 3560-3575
Sarode et al (2020) Reprogramming of tumor-associated macrophages by targeting ß-catenin/FOSL2/ARID5A signaling: A potential treatment of lung cancer. Sci Adv 6(23)

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 2020

- ✓ Full operation of the centralized DZL Data Warehouse, integration of additional databases with periodic updates
- ✓ Prospective sampling of biospecimens and associated clinical data
- ✓ Improvement of the data quality, ongoing harmonization of data
- ✓ Ethical issues (ELSI): Amendment of the broad informed consent forms (with regard to the General Data Protection Regulation), Development of a broad informed consent form for pediatric biobanking, central ELSI consulting established (medical ethics, data protection issues)
- ✓ Training of biobank relevant topics
- ✓ Interactions with DZG biobanks, the German Biobank Alliance and the TMF

Goals 2021

- Implementation of DZL audits, round robin tests and preparations for the certification / accreditation of biobanks (ISO20387)
- DZL data warehouse as a service infrastructure (project planning, provision of samples and data, feasibility)
- Integration of further databases, cohorts and registries into the DZL data warehouse, improvement of the data quality and data depth
- Collection of biosamples and associated clinical data
- Training on biobank-related topics

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Establishment of a biospecimen cohort for research in advanced lung cancer

Lung cancer remains the most common cancer worldwide. Although many different therapies are available today, the sustained efficacy of these therapies is often limited to only a small subset of patients. In many cases among those receiving individual therapy, disease progression inevitably occurs. An important goal of the DZL is therefore to investigate potential mechanisms of resistance development during therapy in various research projects. Tumor tissue from patients is particularly suitable for this approach. Biopsies are obtained as part of routine diagnosis in most cases. However, these biopsies are usually only a few millimeters in size (Figure 1), making it almost impossible to use tissue for research purposes. To foster research on drug efficacy and resistance, a strategy for the collection of biomaterials from patients with advanced non-small cell lung cancer (NSCLC) was first implemented in 2012 across different DZL sites (Figure 2). The concept was to collect biomaterials (tissue and blood) as well as clinical data such as therapy data and questionnaires in a standardized form at all DZL sites and to provide them for various DZL research projects. An interim evaluation of sample and data quality and quantity was successfully published by DZL scientists in 2020. Between 2012 and 2017, approximately 250 patients were included in the cohort. As part of the diagnostic process, additional tissue for research purposes was obtained from approximately 200 patients and immediately preserved at -80°C, as well as blood samples. In addition to the collection of material and data at the time of diagnosis, the patients were followed during their therapy, and tissue and blood samples were also collected during the course of treatment, e.g. when a new biopsy was performed. In total, more than 500 tissue samples and 1200 blood samples were banked by 2017. In addition, over 600 questionnaires were completed. The published data also revealed that the collection

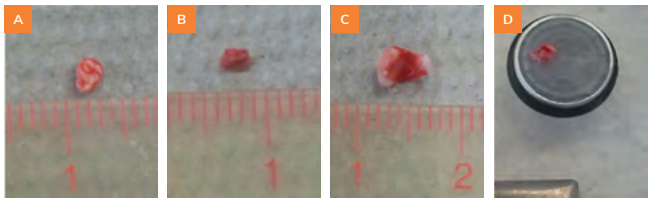


Figure 1
A: CT controlled needle biopsy; B: forceps biopsy;
C: cryobiopsy; D: biopsy storage

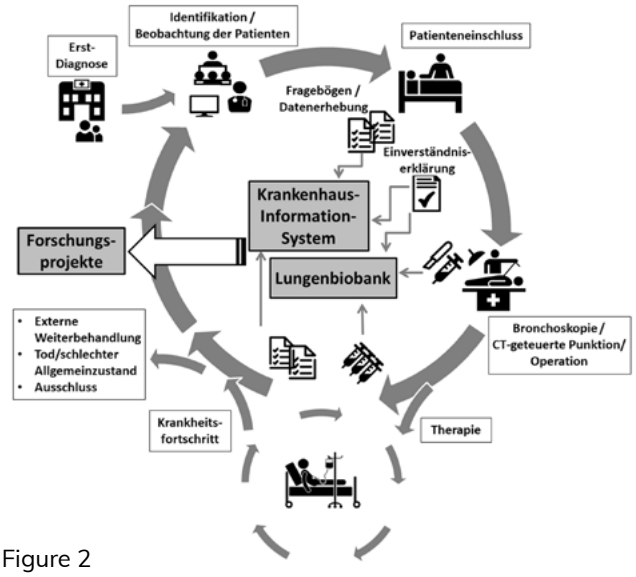


Figure 2

of biopsies, in particular, over the course of the disease was associated with a significant logistical effort as well as a high burden for the patients. Over the course of years, disease diagnostics from less invasive liquid samples (especially blood samples) gained increasing importance. In summary, the cohort described here provides DZL scientists with an extensive collection of high-quality biomaterials and associated data. The collection and preservation of samples and data will continue and be accessible for future questions in the context of lung (cancer) research.

Further Information

Wessels S, Muley T, Christopoulos P, Meister M, Heinzmann-Groth I, Warth A, Herpel E, Hummler S, Klingmüller U, Kuon J, Heussel CP, Eberhardt R, Herth FJF, Winter H, Bischoff H, Stenzinger A, Reck M, Huber RM, Thomas M, Schneider MA (2020) Comprehensive serial biobanking in advanced NSCLC: feasibility, challenges and perspectives. Transl Lung Cancer Res 9(4):1000-1014

Imaging Platform

DZL scientists have access to a wide range of innovative imaging technologies in microscopy and radiology to advance our knowledge of the emergence and development of lung diseases, to evaluate the efficacy of drugs, and to support drug-discovery processes. The Imaging Platform ensures the availability of continuously evolving imaging technologies within the DZL and facilitates the implementation of imaging technologies for research and translation. "Imaging" hereby encompasses technologies of various modalities and with different resolutions and dimensions in preclinical, translational, and clinical applications. The application of Artificial Intelligence (AI) in the field of imaging has a great potential for improving the diagnosis and treatment of patients with lung diseases. So-called deep-learning techniques that enable automated and more complex analyses of data not perceivable to the human eye are at the core of the AI revolution in imaging. Thus, new and complex imaging biomarkers can be generated for the detection, quantification, classification and prognosis of disease outcome. This results in new and far-reaching possibilities to combine these imaging biomarkers with clinical, biological and genomic information and to use them again using AI processes. The development of the necessary AI algorithms and analysis programs is still at an early stage, but they will make an important contribution to personalized medicine in the near future.

Goals Achieved in 2020

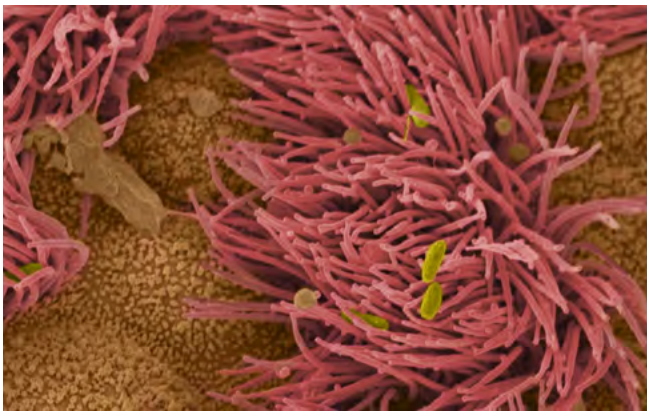
- ✓ Continuation of the imaging technologies portfolio for prospective clinical studies (ongoing)
- ✓ New imaging biomarkers for diagnosis and monitoring of pathological changes of the airways published
- ✓ Strengthening of the interdisciplinary cooperation by organizing a meet-the-imaging expert session at the DZL annual meeting
- ✓ Digital workshop on the subject of AI and COVID-19 imaging
- ✓ Digital workshop on the subject of the Human Lung Atlas
- ✓ Facilitate closer links and transition from preclinical, translational and clinical imaging (ongoing)
- ✓ Introduction of a joint imaging project with the German National Cohort

Goals 2021

- Preclinical and clinical investigation of damaged lung structures in established disease models for better recognition of characteristic change processes of the lung structure and tissue architecture
- Identification of new preclinical biomarkers related to structural tissue damage by employment of 3D imaging technologies
- Advancement of state-of-the-art CT and MRI technologies for the assessment of lung microstructure, alveolar membrane function and regional lung perfusion and ventilation dynamics
- Advancement of computer-aided diagnosis, methods of machine learning and artificial intelligence to improve highly complex image analysis
- Organization of a DZL-wide digital imaging workshop focused on interdisciplinary cooperation across disease areas

Live-cell imaging visualizes how “brush cells” trigger the elimination of respiratory pathogens

The respiratory tract has a mechanism to keep itself clean and thus prevent the development of disease. This self-clearing mechanism is called “mucociliary clearance”. Millions of cilia on the surface of the airway mucosa play a central role in it. Their coordinated beating transports germs, smaller particles and mucus towards the throat. There, these unwanted substances are swallowed, or coughed out, and thus eliminated. To investigate the triggers of mucociliary clearance, scientists measure the activity of the cilia. This is possible using a special microscopic procedure: live-cell imaging. In a collaboration with international physicists, DZL researchers at the Justus Liebig University Giessen (UGMLC site) have optimized live-cell imaging microscopy to measure the activity of cilia. In the procedure they developed, the tracheas of killed mice are removed, opened, placed into a dish and submerged in liquid. The composition of the liquid and the temperature during the microscopic process were adjusted to keep the cells alive and to enable observation of ciliary beating and particle transport in real-time. Using a special camera that captures more than 100 images per second, they showed that ciliary beat frequency can reach up to 25 beats per second. To explore the triggers of mucociliary clearance, the conditions under which the speed of ciliary beating accelerates was tested. The scientists suspected that the invasion of harmful bacteria into the airways would activate the self-clearance mechanism. And indeed, the addition of bacterial proteins, comparable to those made by pathogens, increased the ciliary beat frequency. However, it was assumed that not the cells covered with cilia – the ciliated cells, but their neighbouring cells, called “brush cells”, were responsible for recognition of the proteins and subsequent activation of the cilia. To prove it, the researchers used genetic manipulation to specifically delete certain cell components in brush cells, thereby disrupting their function. When they now added bacterial proteins to the airway mucosa, the cilia were not activated. This result provided evidence for the brush cells’ involvement in the activation of mucociliary clearance. With this approach, the researches elucidated step-by-step the signaling pathway from the recognition of bacterial proteins to the activation of cilia. They also showed that brush cells release the signalling molecule acetylcholine – which is known from nerve cells – to communicate with ciliated cells. Disrupting the function of brush cells by targeted genetic manipulation resulted in mice being more susceptible to infections. Genetic diseases that inhibit the movement of cilia and thus impair mucociliary clearance are also known in humans. Individuals affected by so-called primary ciliary dyskinesis, for example, suffer from frequent airway infections, that can cause long-term damage to the airways. Currently, the DZL scientists in Giessen are investigating whether cells with an analogous function to brush cells also exist in human airways and whether pathological changes in these cells could impair mucociliary clearance.



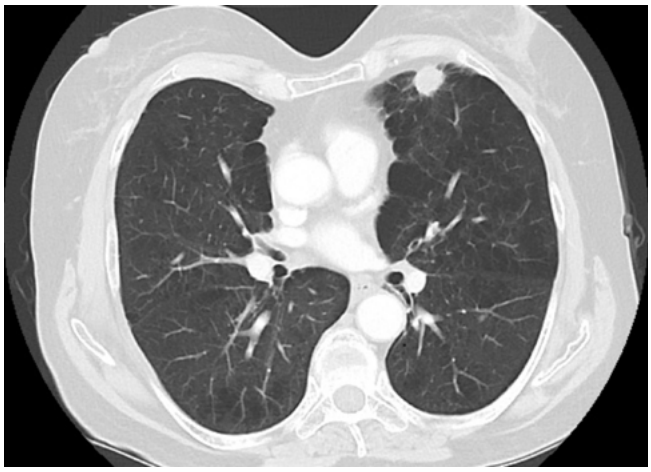
Electron microscopic image of the airway mucosa of a mouse. The cilia are shown in red and cells without cilia in brown. Pathogenic bacteria which can attach to cilia are shown in yellow.

Further Information

Perniss A, Liu S, Boonen B, Keshavarz M, Ruppert AL, Timm T, Pfeil U, Soultanova A, Kusumakshi S, Delventhal L, Aydin Ö, Pyrski M, Deckmann K, Hain T, Schmidt N, Ewers C, Günther A, Lochnit G, Chubanov V, Gudermann T, Oberwinkler J, Klein J, Mikoshiba K, Leinders-Zufall T, Offermanns S, Schütz B, Boehm U, Zufall F, Bufe B, Kummer W (2020) Chemosensory Cell-Derived Acetylcholine Drives Tracheal Mucociliary Clearance in Response to Virulence-Associated Formyl Peptides. Immunity 2(4): 683-699

DZL scientists pave the way to a lung cancer screening program using low-dose CT

Lung cancer is the third leading cause of death in Germany. Since lung cancer initially causes hardly any symptoms, it is frequently discovered in advanced stages when it is less likely to be curable. Detection of tumors in an early stage can save lives, or prolong life. DZL scientists at the Heidelberg site (TLRC) are working to further improve the methodology of the lung cancer screening procedure to advance the implementation of an organized lung cancer screening program for risk groups in Germany. Their expertise was instrumental in the conduct of the LUSI trial. LUSI stands for "German Lung Cancer Screening Intervention" and was initiated by researchers of the German Cancer Research Center (DKFZ) and Heidelberg University Hospital. The trial involved 4052 long-time smokers aged 50 to 69 years. The participants were randomly divided into two groups, of which the first group underwent annual low-dose computer tomography (CT) over a five-year period and the second group did not. As part of the data analyses, researchers addressed the risks of misdiagnosis and overdiagnosis in lung cancer screening. Being wrongly diagnosed with lung cancer brings significant psychological and health disadvantages for those affected. To minimize the risk of misdiagnosis, international researchers have developed models that predict the malignancy of a suspicious nodule, e.g. based on its shape and size. DZL researchers in Heidelberg compared the accuracy of eight prediction models using CT images which were taken as part of the LUSI trial. They discovered that four of these models were excellent in distinguishing malignant from benign tumors. Application of these models in the context of a lung cancer screening program could minimize the risk of misdiagnosis. Lung tumors that would never have been noticed and would never have required treatment without lung cancer screening are referred to as overdiagnosis. This is the case when, without early detection, the patient would have died before lung cancer symptoms would have appeared. DZL researchers investigated the risk of overdiagnosis in the context of the LUSI trial and found that without early detection, about half of all tumors discovered by lung cancer screening would have gone unnoticed for at least four years. To prevent unnecessary interventions, the expected remaining lifetime of people participating in a lung cancer screening program would therefore have to exceed this time. Findings like these help researchers to define eligibility criteria for lung cancer screening programs and to decide whether the benefits outweigh the risks for each individual patient. Based on the results of other international studies, DZL researchers in Heidelberg, together with leading European experts, developed a statement on lung cancer screening. It can serve as a basis for the development of recommendations and guidelines for the implementation of a European systematic lung cancer screening program using low-dose CT.



CT-scan of the lung with suspicious nodule (top right). (Picture Credit: Universitätsklinikum Heidelberg)

Further Information

Becker N et al (2020) Lung cancer mortality reduction by LDCT screening-Results from the randomized German LUSI trial. Int J Cancer 46(6): 1503-1513
Gonzalez Maldonado S et al (2020) Evaluation of Prediction Models for Identifying Malignancy in Pulmonary Nodules Detected via Low-Dose Computed Tomography. JAMA Netw Open 3(2): p. e1921221
Gonzalez Maldonado S et al (2020) Overdiagnosis in lung cancer screening: Estimates from the German Lung Cancer Screening Intervention Trial. Int J Cancer
Kauczor H U et al (2020) ESR/ERS statement paper on lung cancer screening. Eur Respir 55(2):1900506

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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 Dr. Annegret Zurawski, coordinator of the DZL site BREATH (Hanover).

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

The DZL annually allocates a portion of its budget for innovative clinical studies based on the initiatives of DZL scientists (investigator-initiated trials). This funding enables researchers to respond to the latest developments in their field and to further advance such developments as quickly as possible for the benefit of patients. The funds are to be understood as seed capital, enabling a rapid transfer of the latest findings into "first in human" studies.

In the adjacent table the clinical studies currently in progress are listed. Their total funding volume amounted to EUR 1.106 million in the year under review.

For the upcoming DZL 3.0 funding period, 12 applications were received in the reporting year. In the established competitive process, the DZL Clinical Trial Board recommended five of these studies for funding. The DZL Directorate followed this recommendation and a total funding volume of EUR 2.088 million was approved for the next three years.

In addition, DZL researchers can apply for separate funding to finance the preparation and writing of applications for clinical trials, both to the DZL and to other funding bodies, e.g. the DFG or the BMBF. In the year under review, funding for three such applications was approved in the amount of EUR 30,000 each.

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

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

Administrative Coordinator
Dr. Annegret Zurawski (BREATH)

Investigator-Initiated Trials Supported with DZL Funds

Coordinator(s)/ Scientist(s)	Disease Area	Participating DZL Partner Sites	DZL Partner Sites Involved
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
Jobst B	COPD	all	MR-COPD II: Imaging disease progression in COPD
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
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
Vogel-Claussen J	Radiology/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

DZL Collaborations, Partnerships, and Networks

In 2020, within the framework of the German Center for Lung Research (DZL), approximately 2,560 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 took place in Travemünde on January 23-24, at which the entire DZL, including numerous junior scientists, came together to exchange information on the status of their projects. It was the last in-person conference of the DZL to take place before the first lockdown of the corona pandemic in March 2020 (see page 38).

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 on the following pages (see page 38).

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 2,700 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 associated institutions. For instance, together with

CAPNETZ, the DZL has since 2015 been involved in the establishment of the bronchiectasis registry **PROGNOSIS (The Prospective German N**ON**-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 Lung Clinic 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 Lung Clinic 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 three 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 planning.

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 also regularly publishes its news in the journal Pneumologie, the official publication of the DGP, the DZL and the DZK (German Central Committee against Tuberculosis), and is regularly represented at the annual congresses of the DGP (see page 38). 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. For example, in April 2018, DZL researcher and physician Prof. Dr. Michael Kopp was elected president of the GPP, ensuring a high level of exchange between the GPP and the DZL.

Since 2013, the DZL has been a full member of the **Technology, Methods, and Infrastructure for Networked Medical Research (TMF)**, the umbrella organization for networked medical research in Germany. 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 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 page 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 page 38).

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. Dr. Stephen Rennard**, has strengthened the DZL's expertise in the area of industry contacts through his 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.

The DZL Academy promotes 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 provides financial support for courses and conferences, as well as flexible funding for research exchange. The DZL Academy works to ensure 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.

Goals Achieved in 2020

- ✅ Organization of the reception for all DZL Academy Fellows prior to the DZL Annual Meeting
- ✅ Due to the pandemic, the planned DZL Academy Fellow Symposium had to be replaced with a digital lecture program
- ✅ The DZL organized the DZG joint workshop on "Science Communication"
- ✅ DZL fellowships for research stays and in-person training courses have been suspended due to the pandemic and instead were replaced with the sponsoring of participation in the Virtual European Respiratory Society Congress
- ↔️ Relaunch of the DZL Mentoring Program – postponed to 2021
- ✅ DZL Academy Fellow Survey on Digital Format Preferences
- ✅ DZL Academy goes digital (Twitter, Training Platform, ...)

Goals 2021

- Continuation of the digital lecture program
- Organization of a virtual DZL Academy Fellow Symposium
- Funding of training opportunities such as workshops on writing research proposals
- DZL grants for research stays (second half of 2021)
- Relaunch of the DZL mentoring program (second half of 2021)
- Organization of joint DZG activities for the promotion of early career scientists

DZL Academy Board

The DZL Academy Board is composed of researchers, physician 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.

DZL Academy Annual Fellow Reception 2020

For the second year in a row, a reception exclusively for DZL Academy Fellows took place the evening before the DZL Annual Meeting. The event was organized by the five elected Fellows that represent the Fellow community at each site. About 120 early career scientists from all DZL sites used this event in Travemünde for networking and exchange on topics of joint scientific interest and on career paths for basic scientists and clinicians. A science quiz that included questions about the local dialect and customs of people at the site in northern Germany (Kiel – Lubeck – Grosshansdorf) contributed to the relaxed and fun atmosphere.

At the reception, the DZL Academy also officially launched their Twitter platform to disseminate and facilitate information about highly topical research.

Virtual DZL Academy Lecture Program 2020

In 2020, the Academy launched a virtual lecture program. In response to the positive feedback received from Fellows and speakers, the virtual lecture program will now continue indefinitely. At least once a month leading DZL scientists will lecture about current topics in lung research. Afterwards, the fellows have the opportunity to further exchange ideas with the speakers in the question-and-answer session. For many DZL Academy Fellows, moderating these sessions is a first opportunity to moderate a scientific discussion. The pairing of speakers and moderators from different sites ideally promotes the exchange of expertise and the sharing of knowledge in the context of networking. Fellows participate in a survey each year to determine the focus of the lecture program.

Meeting of the DZL Academy Board in January 2020 in Travermünde: Carmela Morrone (CPC-M), Svenja Gaedcke (BREATH), Magdalena Szczygiel (TLRC), Annegret Zurawski (BREATH), Silke Meiners (CPC-M), Birgit Teucher (TLRC), Jörn Bullwinkel (ARCN), Sebastian Marwitz (ARCN), Rory Morty (UGMLC)
Absent: Michael Kreuter (TLRC), Christina Malainou (UGMLC), Claudia Staab-Weijnitz (CPC-M), Carola Voss (CPC-M)

DZG Early Career Scientist Initiatives – How to explain your research?

Each year the German Centers for Health Research (DZG) jointly organise a workshop for early career scientists. The 2020 workshop focused on science communication and took place from 3rd to 5th March at the National Institute for Science Communication (NaWik) in Karlsruhe. 26 participants, six of them from the German Center for Lung Research (DZL), learnt how to communicate their research effectively to different target audiences and developed potential outreach activities for the Berlin Science Week 2020.

DZL – Sponsorship of Conference Participation

Due to the pandemic, the sponsorship program of research stays and scientific exchange at DZL sites had to be suspended. Instead, participation in the virtual annual congress of the European Respiratory Society (ERS) was funded for over 50 DZL Academy Fellows. The ERS congress has become the world's largest gathering of physicians and researchers in the field of pneumology with an outstanding scientific program.

DZG workshop „Science Communication" at NaWiK in Karlsruhe

Equal Opportunities and Diversity

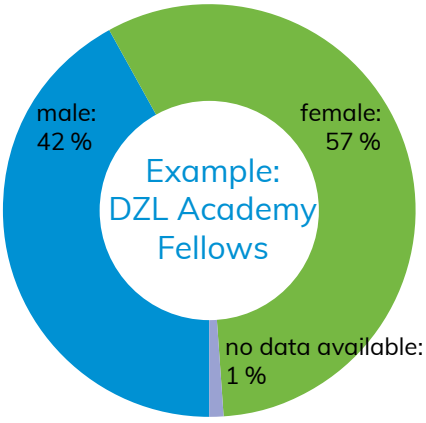
The German Center for Lung Research (DZL) and its member institutions are firmly committed to equal opportunities and equality at the respective DZL sites. For the DZL and its member institutions, it is a fundamental principle that no one should be excluded from a scientific career on the basis of gender, 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 23 %. Read more about this topic under the heading Personnel and Gender Equality on page 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 held digitally in 2020, 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), 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.

Several times a year, the DZL also publishes 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 November 2020.

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 "Publications" shows the latest publications by DZL scientists on a weekly basis. The **image film** of the research network can also be viewed on the DZL website.


Mitteilungsseiten des Deutschen Zentrums für Lungenforschung

DZL

9. DZL-Jahrestreffen in Mannheim – steigende Teilnehmerzahlen und herausragende Nachwuchsförderung

The comprehensive **DZL Annual Report 2019** was published in 2020, again in both German and English. In addition to achievements and highlights of 2019, 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 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, was fortunately a few weeks ahead of the Corona pandemic. On January 23-24, 2020, approximately 500 scientists, clinicians, and early career researchers discussed project results, strategies, and research goals at the **9th DZL Annual Meeting** in Lubeck-Travemünde. The working groups of the disease areas and platforms also took the opportunity for mutual exchange and intensive consultations. For the first time, the Imaging Platform featured a "Meet the Expert" session, where experts provided information on the latest imaging techniques and possible collaborations in the field of lung research at seven stands, some with fully assembled measurement equipment. For the second year in a row, the DZL Academy Fellow Reception took place on the eve of the annual meeting, where young scientists from all sites could network and exchange ideas.

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 of 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 2020 (please see below for more information on 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 clinical trial directory is continuously updated and expanded. By the end of 2020, more than 130 studies had been recorded in the platform.

Lung Information Service

The Lung Information Service (LIS), based at Helmholtz Zentrum München, is an important professional and reliable partner of the German Center for Lung Research (DZL) for patient information. The LIS communicates insights gained directly from research to improve people's health and health literacy. The goal is to provide people with scientifically sound, up-to-date and independent information. In this way, the Lung Information Service helps patients to better manage their complex chronic disease and to take responsibility for their own disease management. In the meantime, an average of 250,000 people per month visit the LIS website for information.

Information is provided in three main ways: via a comprehensive online portal, via events for patients, and via publications ("Fact sheets – The most important facts in brief"). At www.lungeninformationsdienst.de, the LIS offers basic knowledge and new research results in a clear and easy-to-understand way for interested readers. The main topics on the online portal of the Lung Information Service in 2020 were: Asthma Step-by-Step Therapy (January), Coronavirus: SARS-Cov-2/ COVID-19 (February), Bronchitis: Acute or Chronic (March), Lungs and Airways (April), Lymphangioleiomyomatosis (LAM) (May), Biomarkers (June), ARDS – Acute Lung Failure (July), Fit for Everyday Life (August), Long-Term Oxygen Therapy (September), Hyposensitization (October), Clinical Trials (November), and Alpha-1 Antitrypsin Deficiency (December).

At the Lung Information Service, the year 2020 was also marked by the Coronavirus pandemic. Right at the beginning of the pandemic in March, the LIS created a comprehensive website section that focused on topics related to the Coronavirus. In addition, the section featured numerous news articles about the SARS-CoV-2 virus and the

COVID-19 lung disease it caused. The high demand of the population for reliable information on the topic was particularly reflected in more than 190,000 visits to Corona-related web pages, but also in the number of inquiries that reached the LIS. Compared to the previous year, this increased by almost 100 percent.

Due to the pandemic, the LIS also developed new digital formats for its events: In addition to the Patient Forum Lung "Lung Health and Environment", which was still held in person at the beginning of 2020, interested parties were invited to the LIS's first online seminar in the summer of 2020 with the topic "Childhood Asthma". The speaker was Nicole Maison, MD, from the Comprehensive Pneumology Center (CPC-M), at the Munich DZL site.

From 2011 to 2020, the Lung Information Service published more than 1,000 news articles on its website. The main basis for the twice-weekly news are publications on patient-relevant topics in well-known scientific journals. In addition to the purely scientific content, readers also receive up-to-date information on patient-relevant events, recommendations on newly published patient literature, and announcements of interesting TV and radio programs. In addition, the LIS sends out a monthly newsletter to meanwhile more than 4500 subscribers. The Lung Information Service is also active in social media. It has its own Facebook page with more than 4400 subscribers and publishes news from research several times a week via the news service Twitter.

The Lung Information Service receives much positive feedback about the quality and independence of the provided information. In addition, its information is frequently picked up by daily newspapers and other media. In 2020, among others, articles appeared in DIE WELT as well as in widely read local newspapers, including the Münchner Abendzeitung, Ludwigsburger Kreiszeitung or Cuxhavener Nachrichten. Since 2018, the LIS has also published selected articles quarterly in the journal Patientenbibliothek - Atemwege und Lunge (circulation 30,000) in its own LIS section "Lungenforschung aktuell". In this context, DZL scientists are also given the opportunity to provide expert statements. In 2020, these were Prof. Dr. Jürgen Behr (CPC-M), Prof. Dr. Rembert Koczulla (UGMLC) and Prof. Dr. Tobias Welte (BREATH) on the focus topics "Causes of Idiopathic Pulmonary Fibrosis (IPF)", "Pneumological Rehabilitation" and "Prevention through Influenza Vaccination".

Perspectives

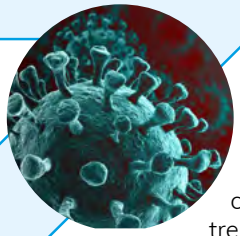
In the future, the Lung Information Service could offer additional services to better address new target groups, especially young people and members of educationally disadvantaged groups. These could include explain videos or podcasts, which could also be disseminated via various social media channels. In order to strengthen the health literacy of people with a migration background, the offers of the Lung Information Service could also be published in other languages(Turkish, Russian) besides German and English in the future. Other target groups to which the Lung Information Service would like to devote increased attention in the future are general practitioners and specialists with a need for pneumological expertise, especially in rural regions.

Patient Lung Forum 2020 in Munich

Selected DZL Highlights of 2020

DZL Researcher Receives 2-Million-Euro Grant from the EU
DZL principal investigator Prof. Dr. Soni Savai Pullamsetti received one of the prestigious Consolidator Grants from the European Research Council (ERC) of the European Union for her excellent research in the field of pulmonary hypertension. Pullamsetti wants to use the EU funds to look for options in which the activated vascular wall cells can be influenced in a way that the progression of the disease could be stopped or even reversed.

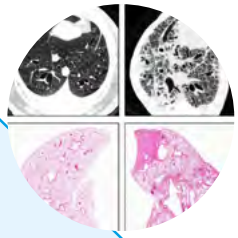
Breakthrough in the Therapy of Cystic Fibrosis
The European Medicines Agency EMA has approved the new triple-combination Kaftrio for the treatment of cystic fibrosis. The approval has been given for specific patient groups aged twelve years and older. It is expected that around 60 percent of cystic fibrosis patients in Germany will be able to benefit from the new drug, which was tested with significant participation from the DZL.



The Dangerous Dual Role of the Immune System in COVID-19
DZL researchers have discovered that the immune system has a decisive influence on the progression of a SARS-CoV-2 infection: Using single-cell analysis, they discovered that the epithelial cells attacked by the virus send a "distress call" to the immune system. However, the immune cells that migrate in response occasionally overshoot the mark: Due to their excessive reaction, they sometimes cause greater damage than the virus itself, as the research group reports in *Nature Biotechnology*.

How SARS-COV-2 Enters the Body
DZL scientists have found that the coronavirus SARS -CoV-2 enters the body probably mainly via two types of nasal mucosa cells. The scientists published their findings, which have implications for developing strategies against the virus to protect against infection, but also for the therapy of people infected with COVID-19, in the journal *Nature Medicine*.

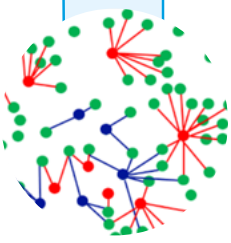
Over 13 Million Euros for New Therapies in Life-threatening Cardiopulmonary Diseases
The Collaborative Research Center on Cardiopulmonary Research (SFB 1213) in Giessen, headed by DZL scientist Prof. Dr. Norbert Weissmann, will be funded by the German Research Foundation (DFG) for another four years. In addition to the Collaborative Research Center at the DZL site in Giessen, the DFG is funding the SFB/Transregio Innate Immunity of the Lung: Mechanisms of Pathogen Attack and Host Defense in Pneumonia led by the Berlin DZL scientist Prof. Dr. Norbert Suttorp, also with participation of DZL researchers from Giessen and Marburg.



Key Processes Identified in the Development of Lung Fibrosis
DZL research groups in Berlin and Heidelberg have succeeded in tracking the development of pulmonary fibrosis in detail. They showed that the NEDD4-2 protein plays a key role in healthy lungs and that the absence of this central regulator is important for various processes in the development of the disease. How lung fibrosis develops and how it progresses can now be studied even more precisely. Based on these findings, published in *Nature Communications*, new therapeutic approaches can be developed.

New Treatment Option for Resistant Cancer Cells
DZL researchers reported in *Nature Communications* on a mechanism that could be used to attack resistant cancer cells. They found that the molecule mTOR, which renders tumors resistant to cancer medications, paradoxically also suppresses a mechanism that is vital for the survival of tumor cells.

Predicting Disease Progression in Lung Cancer
Tumors often contain characteristic accumulations of certain white blood cells, known as macrophages. There are two populations with opposite effects on the tumor: while one is tumor-promoting, the second macrophage population inhibits cancer growth. In a study published in *Cancer Research*, DZL scientists showed that the position and density of the two cell populations in the tumor tissue make it possible to predict the course of the disease. These findings may lead to new therapeutic possibilities.



Clinical Trial on Combination Therapy in COPD: Triple Better than Double
A number of drugs or combinations thereof are available for COPD treatment. The ETHOS trial led by DZL board member Prof. Dr. Klaus F. Rabe tested triple combinations of drugs in comparison with double combinations – with positive results. As the research group reported in the *New England Journal of Medicine*, with the triple combination treatment the number of exacerbations (acute worsening) decreased, the quality of life of the patients improved and the overall mortality decreased by 46 % compared to the double combination treatments tested.

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.

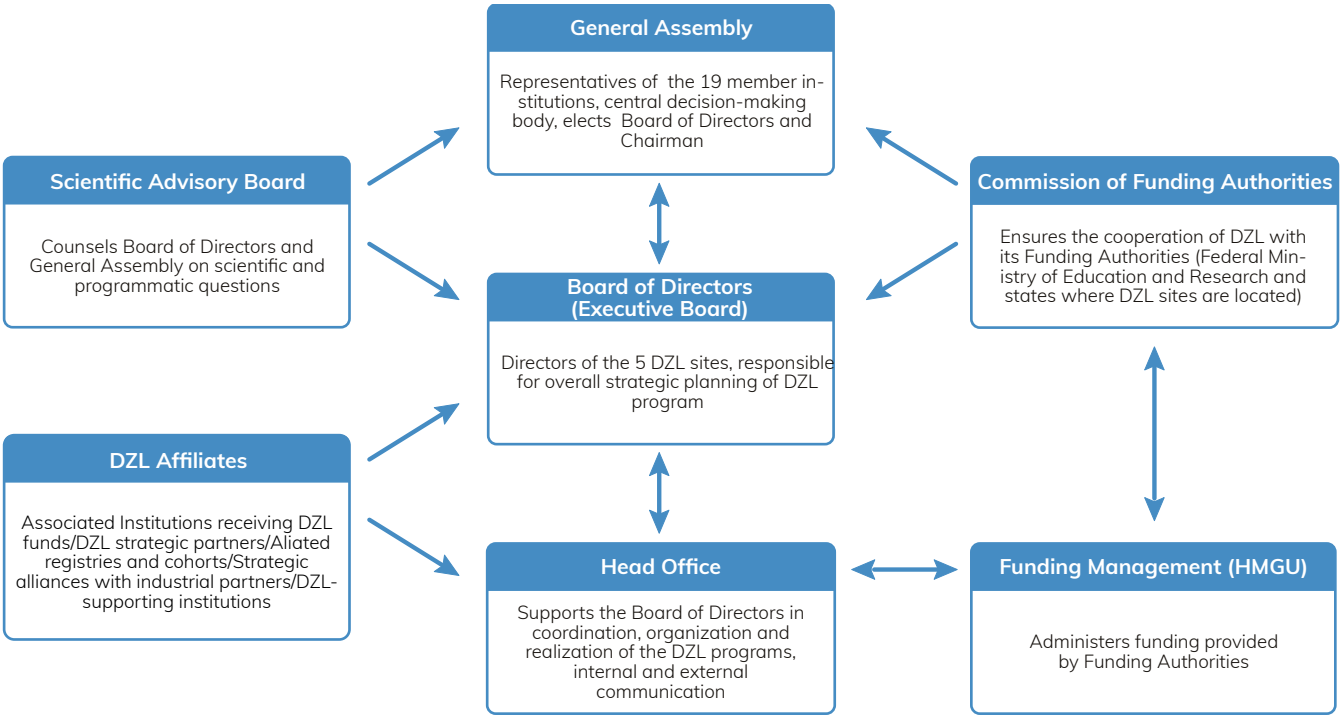
DZG attendance at the German Academic International Network (GAIN) 2018 event

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 2020) 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, among other things, working groups for biobanking, artificial intelligence, data management, promotion of young talent, public relations, prevention, global health and regulatory aspects of clinical studies (stakeholder ability) have been set up. 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 2020, the DZG centers jointly carried out various Corona projects – for example, the establishment of a Europe-wide database for the collection of clinical data and biomaterials from patients with COVID-19 (LEOSS), which provides an important basis for research projects. As part of the promotion of young scientists, a course for young talents in the DZG on science communication was offered last year together with the National Institute for Science Communication. In order to inform the members of the German Parliament about the successful work of the DZG and to exchange ideas with the parliamentarians, a Parliamentary Evening was planned for 2020, which unfortunately had to be cancelled at short notice due to the pandemic. A short image trailer on the DZG and its mission was produced. This trailer is being used, among other things, at online events of the DZG and on the DZG websites. At the beginning of 2019, the jointly designed health research magazine "SYNERGIE" was published for the first time – as a high-quality print product as well as an online edition. Two further issues were published in 2020.

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
- Alina Zidaric, Press and Public Relations

Scientific Advisory Board

The Scientific Advisory Board of the DZL is made up of internationally acclaimed experts in lung research. In 2020 the twelve members of the Scientific Advisory Board were:

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

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

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

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

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

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

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

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

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

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

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

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

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 2020).

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 2020

Name and DZL Site	Prize / Award
Prof. Dr. Soni Savai-Pullamsetti Bad Nauheim	Consolidator Grants des European Research Council (ERC)
Susanne Greve **PD Dr. Christian Herzmann** **Dr. Stephan Rüller** Borstel	Innovation Transfer Prize of the Werner Petersen Foundation
Dr. Panagiota Xanthouli Heidelberg	Research Prize of the René Baumgart Foundation
Dr. Karla Rubio Bad Nauheim	DGP* Research Award for the best paper in the area of basic research
Prof. Ursula Klingmüller Heidelberg	Elected as a member of the European Molecular Biology Organization (EMBO)
Prof. Dr. Uwe Haberkorn **Prof. Martina Muckenthaler** Heidelberg	Appointed as members of the German National Academy of Natural Sciences Leopoldina
Prof. Dr. Uwe Haberkorn Heidelberg **Prof. Dr. Martin Reck** Grosshansdorf **Prof. Dr. Stefan Schreiber** Kiel	Highly Cited Researchers 2020
PD Dr. Karoline I. Gaede Borstel	Re-election to the TMF*** Board of Directors
Dr. Markus Weckmann Lubeck	Johannes Wenner Research Prize of the GPP** and the German Lung Foundation
Prof. Dr. Klaus F. Rabe Grosshansdorf **Prof. Dr. Tobias Welte** Hanover	Honorary Award of the GPP** 2020
Prof. Dr. Martin Reck Grosshansdorf	Appointment to the Scientific Committee for Metastatic Lung Cancer of ASCO****
Prof. Dr. Michael Kreuter Heidelberg	Research Award of the Rosemarie Germscheid Foundation 2020
Prof. Dr. Silke Meiners Munich	Appointment as Editor of the European Respiratory Journal
Prof. Dr. Nikolaus Kneidinger Munich	Rudolf Pichlmayr Prize of the German Transplantation Society
Prof. Dr. Olivia Merkel Munich	PHOENIX Pharmaceutical Sciences Award

* Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin (German Respiratory Society)

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

*** Technologie- und Methoden-Plattform für die vernetzte medizinische Forschung (Technology, Methods, and Infrastructure for Networked Medical Research)

**** American Society of Clinical Oncology

DZL Member Institutions and Sites

Kiel/Lubeck/Borstel/Grosshansdorf

Airway Research Center North (ARCN)
Site Director: Prof. Dr. Klaus F. Rabe

- Christian Albrecht University Kiel
- Research Center Borstel – Leipzig Lung Center
- Lung Clinic 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 Chair 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 Lung Clinic 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, Lubeck, Kiel, Grosshansdorf
Airway Research Center North (ARCN)

Partner Institutions of the Site

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

Prof. Dr. Klaus F. Rabe

- Director of the ARCN DZL Site
- Medical Director of the Lung Clinic Grosshansdorf
- Professor of Pneumology, Christian Albrecht University Kiel
- 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 Lung Clinic 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 Christian Albrecht University in Kiel, who are focused, among other things, 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 Lung Clinic 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 specializing 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
- Acting Vice President and Chief Medical Officer of MHH 2020
- Member of the Internal Advisory Board of the German Center for Infection Research (DZIF) since 2011
- President of the European Respiratory Society 2018/19
- President of the Forum of International Respiratory Societies (FIRS) 2019
- Board Member and Treasurer of the Biomed Alliance since 2019
- President of the Paul Ehrlich Society (PEG) 2018–2020
- Chairman of the Board of Trustees of the CAPNETZ Foundation
- Director of the competence network ASCONET
- 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
- Member of the Editorial Board of the New England Journal of Medicine (since 2006)
- Recipient of the Gottfried Wilhelm Leibniz Prize of the German Research Foundation (DFG)
- Bearer of the Cross of Merit on Ribbon of the Order of Merit of the Federal Republic of Germany
- Fellow of ERS (FERS)
- Director of the Institute of Asthma and Allergy Prevention at Helmholtz-Zentrum München

Contact

DZL Site Coordinator, CPC-M:
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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

Contact
DZL Site Coordinator, TLRC:
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Phone: +49 6221 56-32144

Research Profile
The Heidelberg Translational Lung Research Center (TLRC) is an interdisciplinary center for translational lung research, where physicians and scientists at Heidelberg University Hospital and the Medical Faculty of Heidelberg University, the Thoraxklinik at Heidelberg University Hospital (one of Germany's oldest and largest hospitals specializing in lung disease), and the non-university research centers (the German Center for Cancer Research and the European Molecular Biology Laboratory) all work together to combat lung disease. The common goal is to improve diagnosis and therapy of chronic lung diseases in children and adults by promoting the close collaboration and exchange of expertise between basic research and clinical research. Research is focused on the mechanisms underlying common genetic and acquired chronic and malignant lung diseases, such as Cystic Fibrosis (CF), COPD, and Lung Cancer. TLRC scientists also contribute to research in the fields of Asthma and Allergy, Pulmonary Fibrosis, Pneumonia and Acute Lung Injury, and Pulmonary Hypertension. The scientists' goal is to identify new therapeutic targets to improve diagnostics and develop further curative treatment options. Within the basic research program, cell and animal models are used to investigate molecular causes of chronic airway diseases. Use is made of next-generation sequencing as well as state-of-the-art immunobiology and molecular biology techniques. Current research investigates the mechanisms leading to airway mucus obstruction and chronic inflammation in Cystic Fibrosis and other chronic obstructive pulmonary diseases, such as COPD and Asthma. At the TLRC, systems biology is applied to improve our understanding of the molecular causes of Lung Cancer. The Biobanking and Imaging platforms are crucial to the success of the translational lung research program. Early clinical trials are conducted to make new diagnostic and therapeutic strategies available to patients as early as possible.

DZL Site Giessen, Marburg, Bad Nauheim
Universities of Giessen and Marburg Lung Center (UGMLC)

Partner Institutions of the Site

- Justus Liebig University Giessen
- Philipps University Marburg
- Max Planck Institute for Heart and Lung Research Bad Nauheim
- German COPD and Systemic Consequences – Comorbidities Network (COSYCONET)

Prof. Dr. Werner Seeger

- Chairman and Speaker of the German Center for Lung Research (DZL)
- Director of the UGMLC DZL site
- Director of Medical Clinic and Polyclinic II/Head of the
- Department of Internal Medicine, Justus Liebig University Giessen
- Director, Department of Lung Development and Remodeling, Max Planck Institute for Heart and Lung Research, Bad Nauheim
- Speaker of the Excellence Cluster “Cardio-Pulmonary Institute” (CPI)
- Director of the Institute of Lung Health (ILH) , Giessen
- Fellow of ERS (FERS)

Contact

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Research Profile

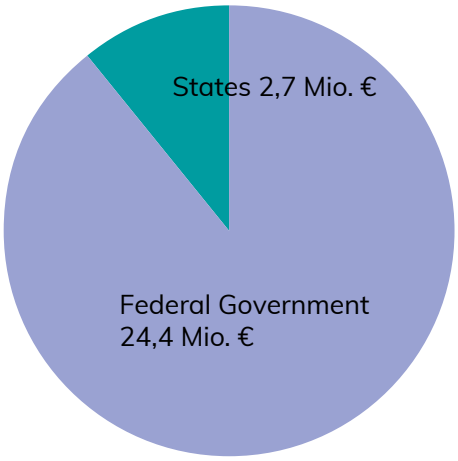
Translational research at the Universities of Giessen and Marburg Lung Center (UGMLC) focuses on lung diseases caused by inflammatory and hyperproliferative processes. This includes research on the impact of environmental factors on the development of asthma and Chronic Obstructive Pulmonary Disease (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

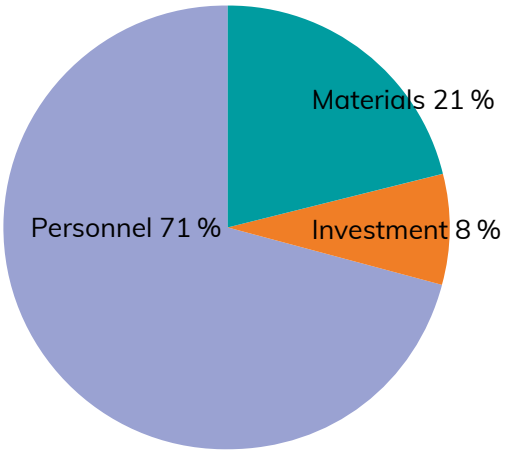
Total Funding and Cost Breakdown 2020

The total funding for the DZL in 2020 was 27.1 million Euros. 90 % was received from the German Ministry of Education and Research (BMBF) and 10 % from the German states with participating DZL centers. Across the eight Disease Areas studied by DZL scientists, around 50 major research projects were supported. Finance is managed by the DZL Funding Management based at the Helmholtz Center in Munich. The Funding Management forwards the project funds to the DZL partner institutions. With the general DZL funding and additional direct funding to the Justus Liebig University Giessen, the BMBF and the state of Hessen Ministry provided 3.0 million Euro funds for establishment of the Institute for Lung Health (ILH) at the Giessen partner site. From 2021 to 2022, the BMBF portion of this budget will be added to the total of DZL funding. (As of July 2021)

Total Funding 2020



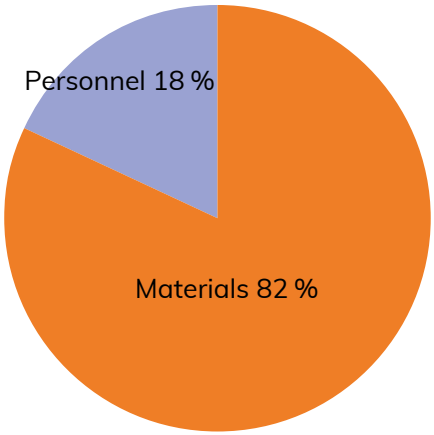
Cost Breakdown: DZL Expenses 2020

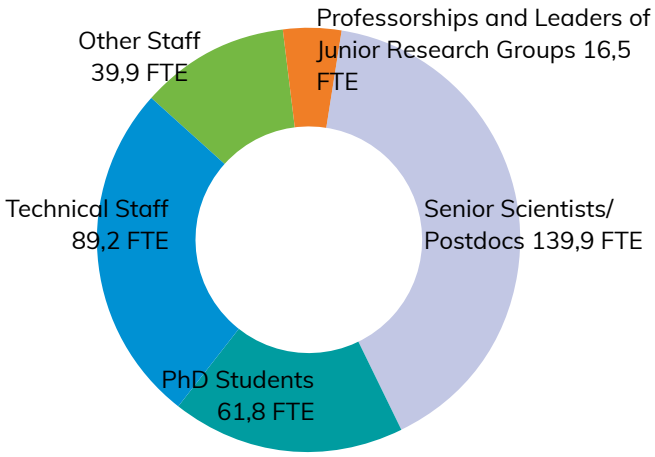


Cost Breakdown: DZL Expenses 2020

The DZL e. V. is financed through membership fees collected from each member institution as well as from donations. Membership fees amounted to € 500,000 in 2020. The 2020 Annual Financial Statement and Year-End Close of the DZL was prepared by the firm Haas & Haas (Giessen).

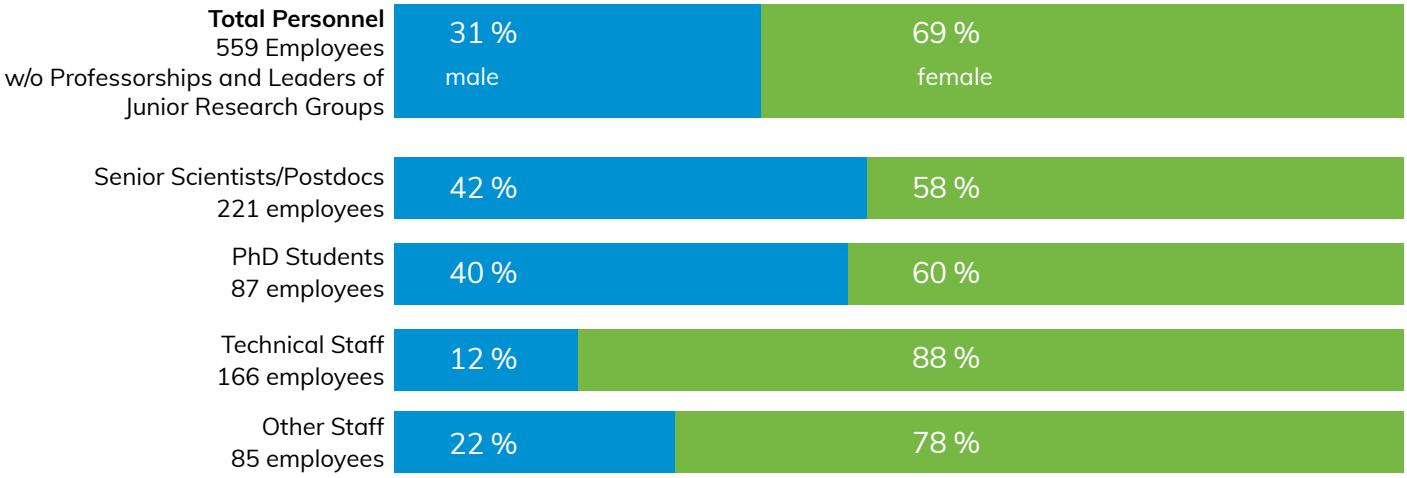
Cost Breakdown: DZL e. V. Expenses 2020





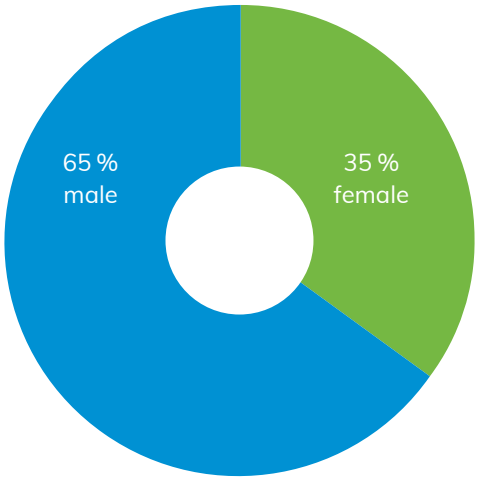
Personnel and Gender Equality 2020

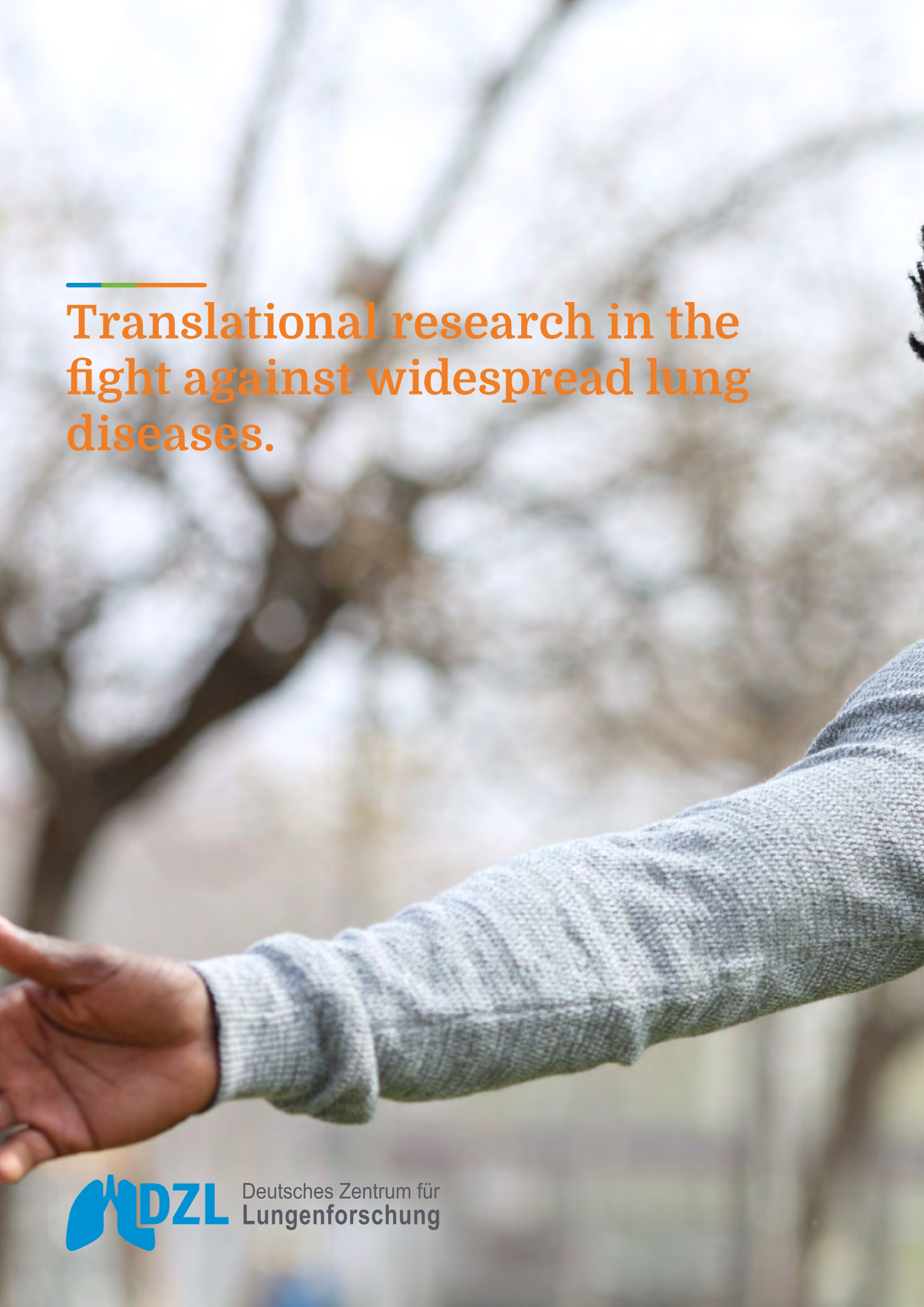
In 2020, employment relationships with 579 persons (347.3 full-time equivalents, FTEs) at the five partner centers and associated partner institutions were funded with DZL money. Of these individuals, 400 were women (69 % of the total personnel).



Professorships and Leaders of Junior Research Groups 2020

In 2020, 20 professorships and leaders of junior research groups were funded within the DZL, 7 of whom are women (35 %).





Translational research in the fight against widespread lung diseases.

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

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