

Synopsis

The FZB is the Lung Research Center of the Leibniz Association. It is dedicated to the research and treatment of inflammatory lung diseases, with a special focus on allergic asthma and tuberculosis (TB). It enjoys increasing international visibility and recognition for the elucidation of mechanisms of asthma predisposition and for the molecular characterization of allergens, allergy-preventive substances and bacterial pathogens. It is internationally renowned for its work on the molecular epidemiology, resistance and pathogenesis of TB and the individualized optimization of antibiotic therapy in M/XDR-TB patients. The FZB is the headquarters of the National Reference Centre for Mycobacteria and the Supranational Reference Centre of the WHO.

The FZB carried out an extensive **structural change** at the beginning of 2012. The aim was to abolish departments based purely on disciplines and to introduce content-driven program areas that map cooperative and interdisciplinary strands of action, ranging from basic research to model systems and clinical application. The total of 20 research and junior research groups, which work on projects and develop special topics, were reallocated to **two priority research areas** ("**Asthma and Allergy**" and "**Infections**") in accordance with their contribution to the agenda of the strands, each of which is strategically aligned by a program director with the overall mission of the Lung Center. An **infrastructure area "Medicine"** provides the necessary facilities (medical clinic, medical care center, pathology, biobank, study center), which enable bidirectional translation, and is headed by the Medical Director. Together with these three directors, the CEO of the Center develops the overall strategic orientation of the Lung Center and interacts with the supervisory and funding bodies.

In the years 2015-2017, the FZB published 464 with a total of 3,180 impact factors (IF). While in the years before 2012 there were only a few **publications** in high-ranking journals at the FZB, in the current reporting period 79 publications had an IF of more than 10 (including 6 New England Journal of Medicine, 4 Lancet Infectious Diseases, 2 Nature Genetics, 3 Nature with an IF>20). The proportion of high-ranking publications (IF>10) at the FZB rose continuously and reached a quota of 20% of all publications in mid-2018; 6% of publications now (2018) have an IF > 20.

The FZB is funded extensively and on a long-term basis by **third-party funds** (total volume: 22.23 million euros, 2015-2017), among others in the German Centres for Health Research (DZL and DZIF), in other BMBF collaborations (EXASENS, Glutevis, ANTI-TB, TB-SeqDisk, Lipidomics Informatics for Life Science-LIFS, TB-Sequel), EU consortia (NAREB, AnTBiotic, ERANET-LAC, EUseqMyTB), foundations/NGOs (ReseqTB, Cryptic, TBNET) and in the Cluster of Excellence (2007-2018: Inflammation at Interfaces; 2019-2025: Precision Medicine in Chronic Inflammation) and in regional and national DFG collaborations (SPP 1580, IRTG 1911, GRK 1727). The third-party funding raised for the year 2017 amounted to 48.6% of the total funding by the federal and state governments.

The FZB is a lead institution in **Leibniz agendas** (Leibniz-Wissenschaftscampus EvoLUNG with the CAU Kiel and the MPI in Plön; Leibniz Research Network INFECTIONS `21 and Leibniz Research Network Health Technologies, Leibniz Center Infection with Bernhard-Nocht-Institute and Heinrich-Pette-Institute in Hamburg, Leibniz Competition (Networking) "Airway microbiota" with Leibniz Institutes Photonic Technologies in Jena and German Collection of Microorganisms and Cell Cultures in Braunschweig and TU Munich) and has 9 professors appointed jointly with the universities in Lübeck and Kiel.

Between 2015 and 2018, scientists, physicians and biology laboratory assistants at the FZB received a total of 18 supraregional prizes and awards, including the Wissenschaftspreis des Stifterverbandes für die deutsche Wissenschaft, den Memento-Forschungspreis für seltene Erkrankungen, einen Exzellenz-Chair des Landes SH, den Hauptpreis der Deutschen Gesellschaft für Hygiene und Mikrobiologie, den Leibniz-Auszubildendenpreis, den Gertrud-Meissner-Preis der European Society of Mycobacteriology, den Nachwuchsförderpreis der Deutschen Gesellschaft für Allergologie und klinische Immunologie, den Bencard Next Generation Award, den Kanert Preis für Allergieforschung und den Leibniz-Gründerpreis.

The FZB operates its own Medical Clinic to implement its translational research agenda (as the only institute of the Leibniz Association). It is one of the few hospitals in Germany to participate in both the German Centre for Infection Research and the German Centre for Lung Research. The clinic has two internal-pneumological wards, an intensive care unit/intermediate care ward, an infection station and a sleep laboratory (a total of 83 beds, approx. 3000 patients per year). The BioMaterialBank Nord at the Medical Clinic is a member of the North German Biobank Alliance. The pathology at the Research Center Borstel is operated as a combined pathology together with the University of Lübeck and the University Hospital Schleswig-Holstein.

The FZB is internationally networked (134 cooperation agreements) and actively operates partner laboratories at the "University of Namibia Medical School" in Windhoek and at the University of Xiamen (China).

The FZB has a **modern center culture**, in which the compatibility of career and family as well as good scientific practice are sustainably anchored:

The FZB operates a campus kindergarten, has flexible working hours and home office arrangements, and has systematically anchored equality aspects in all resource and staff decisions. 2018, 33% of the scientific management positions (including research and junior research groups) were held by women. There is a female director on the four-member Board of Managing Directors and three out of nine members of the extended Board are women.

The "Borsteler Model" consisting of a culture of error learning for the sustainable safeguarding of **Good Scientific Practice** has become a role model for the efforts of the Leibniz Association to conduct a sustainable discourse on the framework conditions for Good Scientific Practice at the institutes.

Since 2005, the FZB has contracted a professional consulting and exploitation agency (Ascenion). At the end of 2017, the FZB held 28 **patents and licenses**. In its analysis in 2015, the externally supervised workshop "Enabling Innovation" came to the conclusion that the FZB, in comparison with similar research institutions of the Leibniz Association, has established a highly advanced innovation culture. Between 2015 and 2017, the FZB generated a total of 204,000 Euros in realization proceeds.

The highlights of FZB research in terms of content in recent years:

Hydrophobic/lipophilic peanut allergens have been discovered as new allergen classes. Component-resolved diagnostics in combination with innovative functional test methods (e.g. basophil activation test) leads to higher specificity and thus to effective and targeted risk and therapy management in patients with complex allergies and under treatment with biologicals.

In the non-invasive ventilation of COPD patients, a modification of a ventilator (patented annual revenue of at least 70,000 Euros) can achieve a sustainable improvement in the quality of life of patients in the final stage of COPD.

The importance of lipoteichoic acid for the virulence of Pneumococcae was redefined and a peptide toxin from *Candida albicans* (candidalysin) was elucidated with regard to its antibiotic properties.

Based on pioneering work at the FZB, the basis was created for the establishment of genome-based methods for high-resolution molecular biological pathogen surveillance. Using "Next Generation Sequencing", the genetic material of the pathogens can be decoded and reliably used for the analysis of local and international outbreaks within a few days.

The application of pathogen genome-based diagnostics for MDR-TB patients at the Medical Clinic Borstel is unique. The genome sequencing of the pathogen makes it possible to conceive individualized antibiotic therapy regimes and the use of "biomarkers of recovery" to shorten MDR-TB therapy individually. A partner laboratory has been set up at the University of Windhoek (Namibia) to implement and test molecular resistance diagnostics on samples of patients from the Katatura Hospital. This will establish and evaluate the possibilities of individualized TB therapy for M/XDR-TB patients in a high-incidence country and make them usable as a model for other countries.

Based on these achievements, the FZB has developed an ambitious **program for the future**. The priority research area Asthma and Allergy focuses on: (i) Development of primary prevention strategies to reduce the incidence of asthma/allergy. Among other things, this will be done by identifying and applying protective microbial metabolites and using transgenerational models of the risk of asthma, (ii) predicting the severity of allergic reactions using individual sensitization profiles and marker allergens; Further development of biomarker signatures for distinguishing asthma phenotypes and predicting therapy responses, (iii) co-development of a diagnostic chip for predicting asthma and COPD exacerbations and the severity of an allergic reaction, (iv) cross-program evaluation of the microbiome as a possible starting point for host-oriented therapies; development of a carrier system of peanut marker allergens for epicutaneous-specific immunotherapy.

The questions on the structure and function of the human lung microbiome and in the mouse model, which are currently primarily dealt with in the priority research area within the framework of collaborations, are to be strengthened in future by a W3 professorship "Functional microbiome research in chronic lung diseases", which will be established jointly with the University of Kiel.

Over the next 7 years, the priority research area Infections will contribute to (i) significantly shortening the duration of TB therapy, (ii) establishing NGS-based individualized antibiotic therapy of M/XDR-TB as the gold standard in emerging countries, (iii) genome sequencing of clinical *M. tuberculosis* strains as a standard tool for TB surveillance, (iv) to identify new target structures for drugs or host-oriented TB therapy, (v) to optimize nanocarriers as a form of administration of antibiotics, and (vi) to evaluate the microbiome as a possible starting point for host-oriented therapies.

The research on non-tuberculous mycobacteria will be strengthened by a W2 professorship, which will be jointly appointed with the University Hospital Eppendorf (University of Hamburg).

The FZB considers a strategic extension of the scientific portfolio to the fields of COPD and microbial research to be necessary. To this end, it is planned to apply for a **kleinen strategischen Sondertatbestands ("environmental microbiome lung health")**:

Conceptually, there will be systematic comparative studies on the pathogenesis of chronic lung diseases (such as asthma, TB and COPD) based on the microecology of the lung. New therapeutic strategies developed from this should prevent the worsening of the disease or alleviate the consequences of the treatment of severe forms, e.g. COPD. In detail, six "innovation groups" limited to 5 (+2) years and two infrastructure platforms are to be set up from 2021. On the one hand, these groups will build on the structural-biological and metagenomic expertise in the field of infections and, on the other hand, strengthen the ongoing further development of the priority research area Asthma and Allergy in elucidating the role of lung microbiom in civilisation-associated inflammations of the lung. In addition, a systems medical platform ("Data Science") should enable an integrative examination of the influences and interactions that are significant, among other things, in the progression or healing of TB, but also in the exacerbation of COPD infections. In addition, an own expertise in epidemiology and biostatistics should ensure the implementation studies.

The strategic aim of the Sondertatbestand is to use the cross-sectional agenda "Evolutionary Medicine", which is already well established in the research landscape of Schleswig-Holstein, with a core topic of "Microbial Research" as a guiding beam for the joint further development of the priority research areas and to focus on COPD research relevant for patients of the Medical Clinic.

In recognition of the supraregional importance of the Leibniz Lung Centre 2015/2016, the grant authorities have decided to equip the FZB - which has long suffered from an outdated structural infrastructure - with modern research infrastructures (new central laboratory building with S3 unit, animal breeding and keeping, new National Reference Center for Mycobacteria), the construction of which will cost a total of at least 53 million Euro and be completed in 2021/2022. A master plan is in progress, which will also provide the remaining outdated laboratories of the structural biology units with new premises until approx. 2027. This means that the FZB will be well positioned for the coming decades in terms of its infrastructure.