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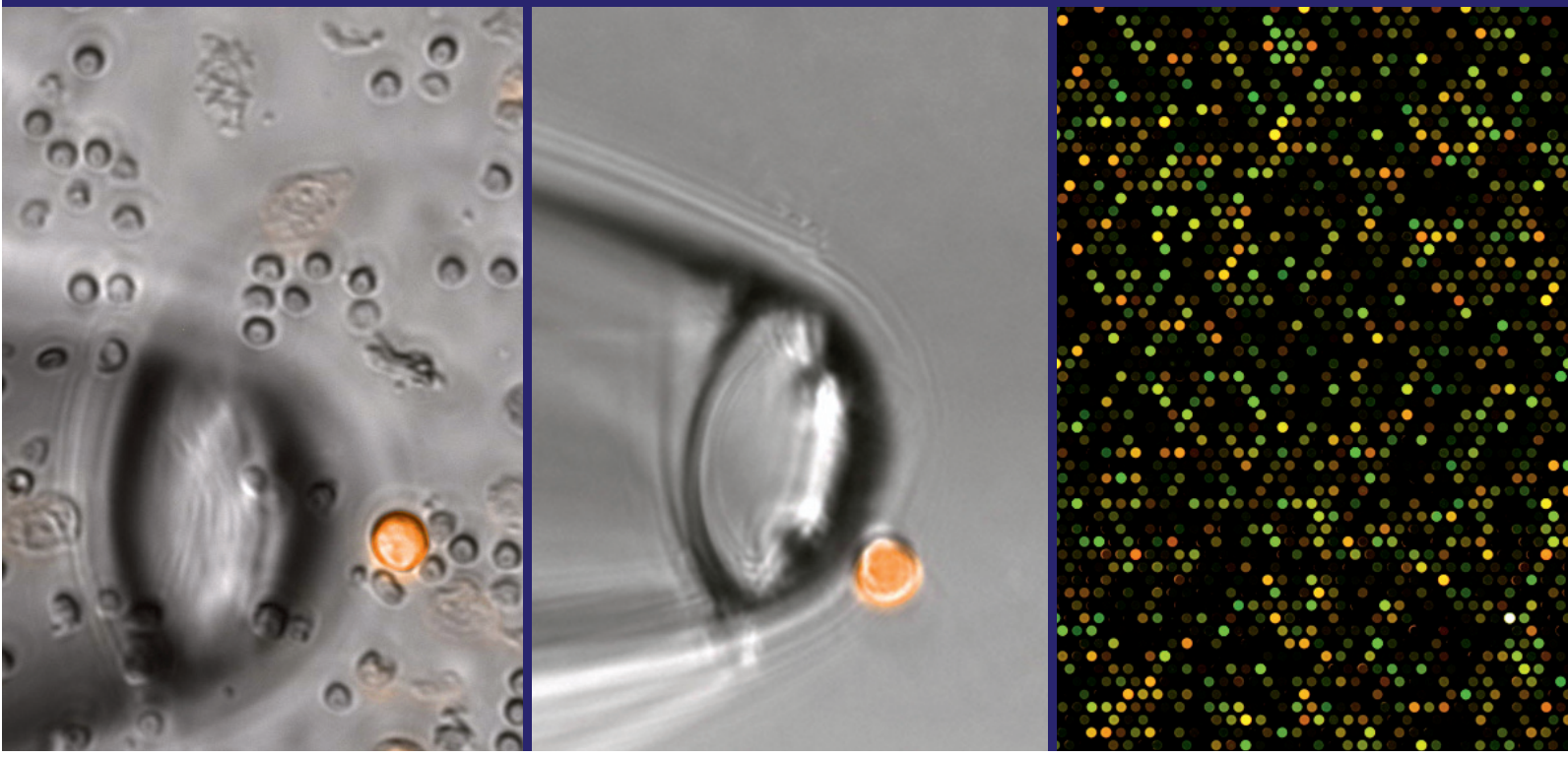
FRAUNHOFER INSTITUTE FOR TOXICOLOGY AND EXPERIMENTAL MEDICINE ITEM

NEWS REPORT

JANUARY 2012



The project group in Regensburg is focused on cancer cells. The sequence of images shows the isolation of a breast cancer cell (orange) and, on the right-hand side, an excerpt from its "molecular portrait" – different levels of gene activation point to certain cell properties.

NEW PROJECT GROUP FOR PERSONALIZED CANCER THERAPY

Since 2011, the Fraunhofer Institute for Toxicology and Experimental Medicine has a new working group at the University of Regensburg: based in Regensburg's BioPark, the project group "Personalized Tumor Therapy" is being set up under the leadership of Professor Christoph Klein. The group was jointly initiated by the Fraunhofer-Gesellschaft, the *Land* Bavaria, and the University of Regensburg, where Klein has been Head of the Division of Oncogenomics for several years already and has been holding the Chair of Experimental Medicine and Therapy Research since 2010. His focus is on basic research into the formation of metastases. The aim of his research is to understand what kind of tumor cells can develop into metastases and why some cells survive for years after tumor resection in a microenvironment that is alien to them, without growing into dangerous metastases. By studying the tumor cell genome with cutting-edge methods of molecular biology, the scientists are trying to unravel the mystery of these threatening cells, with the aim to systematically defuse potential founder cells of metastases. Application-oriented basic research and the translation of its results into novel diagnostic and therapeutic methods nicely fit the concept of the Fraunhofer-Gesellschaft, one of whose flagships is translational research. Read more about the research activities of the Regensburg team and the objectives pursued by the head of the group, Christoph Klein.

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EDITORIAL

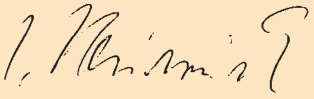
Dear Reader,

Among our aims at the Fraunhofer ITEM is to contribute to the development of novel diagnostic and therapeutic approaches, our focus being on inflammatory and allergic conditions of the lung. Last year, cancer research also became an issue here. By means of a Fraunhofer project group at the University of Regensburg, drug research and development at the Fraunhofer ITEM are being enhanced. We are pleased that the renowned researcher Professor Christoph Klein will be setting up a project group on "Personalized Tumor Therapy". These research activities have been made possible through financial support from the *Land* Bavaria and the strong interest of the University of Regensburg. You will find more about this in this News Report.

Furthermore, we will give you some insight into other current activities: the Division of Pharmaceutical Biotechnology in Braunschweig has moved into new and even better equipped facilities, construction of the new center for early-phase clinical studies – the CRC Hannover – is on schedule, and ongoing studies in the Department of Clinical Airway Research show that new facilities as will be available in the CRC Hannover are much wanted. In addition, you will find an update on our activities to develop novel diagnostic methods for COPD.

I hope you will enjoy reading this issue.

Yours sincerely,



Prof. Dr. Dr. Uwe Heinrich
Executive Director

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News Report spoke with the head of the new project group, Professor Christoph Klein:

What will be the focus of your research in Regensburg's BioPark?
Klein: The aim of this project group is to use the information obtained by molecular analysis of disseminated and circulating tumor cells to develop novel diagnostic tests and new therapies. The steps leading to this goal are manifold, ranging from novel techniques for the detection and isolation of disseminated and circulating tumor cells to their genome-wide molecular characterization and to the development of pre-clinical therapeutic models with expanded and disseminated tumor cells.

What will a personalized tumor therapy based on these investigations look like?
Klein: Most patients diagnosed with cancer today have not yet developed any metastases at the time of diagnosis, which means that they can potentially be cured. Depending on tumor type and stage, many patients will receive adjuvant therapy after surgical removal of the primary tumor, that is, an accompanying systemic treatment (in most cases chemotherapy). This treatment is selected empirically according to the principle of trial and error in large clinical treatment studies. This method swallows huge amounts of money and time, while its efficacy is limited. We would like to make this process more rational by first conducting a precise molecular analysis of the target cells of the adjuvant therapy, to identify patients who will or will not respond to this treatment. At the same time, every molecular detail of these cells may potentially provide targets for novel therapeutic approaches. Strictly speaking, personalized tumor therapy would consist in the attempt to find the right medications for treating the early-stage systemic disease of a particular patient, so as to actually prevent the formation of lethal metastases.

What chances do you see for therapies against disseminated tumor cells to be actually developed in the foreseeable future?
Klein: There is still a lot for us to learn, but if we manage to find partners with whom we can analyze the target cells of therapy in early-phase clinical treatment studies, we may be able to progress faster than seems likely at present. We may even find that there are among the large number of already approved pharmaceuticals a couple of medications that are particularly well suited for this approach, but have never been tested. In this case, we may make unexpectedly good progress.

"Nobel prize in cancer research"

In 2011, the renowned Dr. Josef Steiner Prize, also referred to as "Nobel prize in cancer research", was awarded to Professor Christoph Klein. He received the prize for his basic research into the spreading of cancer cells and the formation of metastases. Since mid-2011, Professor Klein has been setting up the newly founded Fraunhofer Project Group in Regensburg, which is assigned to the Fraunhofer ITEM in Hannover. The prize, endowed with one million Swiss francs, is shared by Professor Klein and the cell biologist Dr. Eduardo Moreno from Bern, Switzerland.

Christoph Klein studied medicine at the Ludwig Maximilians University (LMU) in Munich. He did part of his PhD research work in Canada at the Ontario Cancer Institute and thereafter returned to LMU Munich. Having been awarded the BioFuture prize of the German Federal Ministry of Education and Research, he worked as group leader at the LMU Institute of Immunology from 2001 to 2006. In 2004, he qualified as professor in Immunology at the LMU Faculty of Medicine. From 2006 to 2010, Christoph Klein was Head of the Division of Oncogenomics of the University of Regensburg, where he has been holding the Chair of Experimental Medicine and Therapy Research since 2010.

COPD: EASIER DIAGNOSIS IN THE OFFING

About four million people in Germany suffer from severe chronic bronchitis (COPD), most often as a result of smoking. The earlier this respiratory disease is diagnosed, the better the chances for treatment success. While so far patients have to endure bronchoscopy to obtain an accurate diagnosis, a new method might enable non-invasive and thus less stressful examinations in the future. Scientists of the Fraunhofer ITEM, physicians of the Hannover Medical School, and experts in fluid mechanics of the Leibniz University of Hannover and the University of Aachen (RWTH) are collaborating to develop a non-invasive method for diagnosing and monitoring the course of COPD, that is, without the need to introduce a tube into the patient's trachea: they are analyzing the patient's exhaled breath and the droplets (aerosols) it contains.

Measurement of aerosol particles

In the future, the size and number of aerosol particles or droplets in exhaled breath condensate are to be used as indicators of the health status of the lung. To enable this new approach, the scientists first had to systematically explore the characteristics, formation, and transport of the droplets, and in what way these depend on the condition of the lung. The fundamental investigations in this regard were performed at the Fraunhofer ITEM. The aerosol researchers developed a measurement system allowing particles in exhaled breath to be accurately analyzed. Measurements in healthy volunteers and in patients suggest that the particle size distribution may enable early detection of pathological changes in lung structure as observed in COPD. Based on the collected data, the fluid mechanics experts of the Leibniz University developed a simulation model. This model shows what happens in the lower airways leading to droplet formation: when breathing in, the walls of the small alveoli move apart, causing the liquid film lining the alveoli to disrupt and release the droplets that can then be measured during exhalation.

The impact of gravity

How many particles are actually generated deep down in the lung and what fraction will normally fall victim to gravity? Aiming to understand the processes in detail and to place the analysis of breath condensate on a firm footing, the ITEM researchers have been exploring this question as well. They want to provide evidence that the observed differences in the size spectrum of exhaled particles between healthy subjects and COPD patients are a result of changed lung structure – and thus of deposition processes due to gravity. To provide this evidence, it is necessary to escape gravity. And this is what the researchers did. They participated in parabolic flights performed by the German Aerospace Center, during which zero-gravity is achieved several times for 22 seconds each. During this time, particle distribution in the exhaled breath of smokers and persons with mild COPD was measured. Even though not all measurement results have, as yet, been analyzed, the scientists are confident that patients with respiratory diseases will be able to benefit from this research in the not too distant future.

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NEWS IN BRIEF

Commended:
Best presentation

*"Best Oral Presentation Award" is the prize won by **Katharina Schwarz** (see photo), scientist of the Fraunhofer ITEM Department of Aerosol Technology, during this year's congress of the International Society for Aerosols in Medicine. Her lecture about the characterization and analysis of aerosols in exhaled breath was selected from among over 150 presentations. For her experiments, Katharina Schwarz has already taken off into the air several times to circumvent the influence of gravity. For more information, please refer to the article to the left.*

Moved in: Biotechnologists in new facilities

The staff of the Fraunhofer ITEM Division of Pharmaceutical Biotechnology are happy with their new facilities on the Braunschweig campus of the Helmholtz Center for Infection Research. The roughly 50 employees, who in the past were dispersed across four different buildings, finally benefit from short distances. Besides a 700-m² floor with office and meeting space, they now have at their disposal two and a half floors with a total of ca. 2000 m² of laboratories and pilot plants for process development and scale-up plus 600 m² with clean rooms of classes D and C for GMP manufacture of biopharmaceutical active ingredients by means of microorganisms and animal cells. In addition, the existing clean-room area has been enlarged by a class-B clean room, where investigational medicinal products can be manufactured and filled into vials and ampoules under sterile conditions.

Published: New method under prevalidation

To predict health risks from inhalation of gases, researchers to date have to resort largely to animal experiments. In a cooperative research project funded by the German Federal Ministry of Education and Research and coordinated by the Fraunhofer ITEM, an in-vitro test system was explored where the gases are passed over human lung cells. The cultivation method for these cells simulates the air/liquid interface in the lung. The results obtained in four different laboratories showed good agreement with the findings from animal experiments. The German Federal Institute for Occupational Safety and Health (BAuA) has now published the results in a report entitled "Prävalidierungsstudie zur Prüfung der toxischen Wirkung von inhalativ wirksamen Stoffen (Gase)", which can be downloaded (German only) at www.baua.de/publikationen.

On schedule: CRC Hannover under construction

Those who regularly pass by the big construction site of the CRC Hannover in Feodor-Lynen-Strasse can see that the construction works for the new clinical research center are progressing fast. Starting in fall 2013, safety and efficacy tests with new medications that have not yet been approved for commercial use are to be conducted in this new building. The CRC Hannover is a joint project of the Fraunhofer ITEM, the Hannover Medical School, and the Helmholtz Center for Infection Research.

ASSESSING THE HEALTH RISK FROM WATERPROOFING SPRAYS

The use of consumer sprays such as waterproofing sprays has been repeatedly reported to result in acute lung injury in consumers. Manufacturers of raw materials and bottlers as well as those in charge of consumer protection, therefore, require the health risk from the use of such spray products to be assessed in advance. To this end, Fraunhofer ITEM scientists have developed a holistic strategy for screening of sprays that contain surface-active agents.

To characterize the exposure, the spraying process was simulated in a way that closely mimics the common application process, and the respirable fraction of the aerosol released into the indoor air was measured. Acute lung toxicity was tested in the isolated perfused lung (IPL) of the rat. Using a standardized nebulization protocol, the inhaled dose was determined and a variety of respiratory parameters were monitored.

Trials with ten ready-to-use spray products enabled a clear differentiation of exposure potentials depending on the spraying technology used. Worst results were obtained for gas-propelled spray formulations. For seven of the investigated substances, analysis of the IPL tests revealed significant changes in the parameters tidal volume, compliance, and resistance as compared to controls. All in all, there was an excellent correlation between the results of this test and in-vivo findings. In the future, tests in the isolated lung could be performed before any testing of a substance in living animals is undertaken, to allow formulations exhibiting acute lung toxicity to be identified and discarded in advance.

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PILOT STUDY: GRASS POLLEN AND ATOPIC DERMATITIS

About four million people in Germany suffer from atopic dermatitis, most of them children. There are many factors triggering the disease – stress can play a role, but also pollen and other allergens. Grass pollen in particular has been observed again and again to cause symptoms to flare up in sensitized patients with atopic dermatitis. Scientific evidence for this observed correlation has yet to be provided, and this is what scientists of the Fraunhofer ITEM Department of Clinical Airway Research are now aiming for. In an ongoing double-blind, placebo-controlled study with parallel groups, performed in collaboration with the Hannover Medical School Clinic for Dermatology, Allergology and Venerology, they are exploring the effects of grass pollen exposure on the skin condition in patients with atopic dermatitis.

For their experiments, the scientists make use of the Fraunhofer Environmental Challenge Chamber – ECC for short –, which allows the natural pollen flight to be simulated under controlled conditions. If this study demonstrates that grass pollen exposure in the Fraunhofer ECC leads to a significant worsening of the skin condition in patients with atopic dermatitis, the scientists would not only have provided scientific evidence for the above hypothesis, but would also have at their disposal a new model for drug trials: controlled deterioration of the skin condition could then be used to test the safety and efficacy of novel medications for treating atopic dermatitis.

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NOVEL BIOMARKERS FOR DIAGNOSIS AND THERAPY

For both clinical diagnostics and clinical trials of the pharmaceutical industry, there is an increasing need for specific molecular biomarkers that enable effective diagnoses. They will contribute to early detection of diseases and individualized treatment – and will thus provide the basis for more personalized medicine.

With RIBOLUTION (Innovative Ribonucleic acid-based Diagnostic Solutions for Personalized Medicine) a cross-disciplinary research program in the area of molecular diagnostics was started in 2011 under the leadership of Professor Friedemann Horn from the Fraunhofer IZI. Five Fraunhofer institutes, one of which is the Fraunhofer ITEM, have teamed up to explore a novel class of molecules with a great but, as yet, largely unexploited potential for use as biomarkers: non-coding RNAs (ncRNAs).

The Fraunhofer ITEM is bringing in its clinical expertise in the area of COPD. As part of the RIBOLUTION project, a Fraunhofer COPD cohort with different severities of the disease will be set up and characterized, and the potential of ncRNA biomarkers will be analyzed in this group. Furthermore, in cooperation with GlaxoSmithKline the potential of ncRNA markers will be studied and validated in a large existing and already characterized COPD cohort, the ECLIPSE cohort.

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