

# Walking the Line between Research and Practice

The advances made by **Werner Seeger** and his team in the treatment of pulmonary hypertension mean that many patients at least live longer, with a better quality of life. This, however, is not enough for the Director at the **Max Planck Institute for Heart and Lung Research** in Bad Nauheim: the dedicated doctor and researcher wants nothing less than a full cure for this disease.

TEXT **KLAUS WILHELM**

**A**lmost every morning at around 7:00 a.m., a man cycles five miles through the hilly fields of central Hesse from the small municipality of Biebertal to the somewhat bigger town of Giessen. Spring, summer, fall and winter. Not even sub-zero temperatures and snow-covered paths and streets can deter him. After all, he has spikes for the wheels. He stops his vehicle at the Director's parking spot at the Hospital for Internal Medicine at the Giessen campus of the University Hospital of Giessen-Marburg. The man is the Director and one of today's most renowned lung specialists.

## THE MIRACLE OF BREATHING FREELY

Werner Seeger, a tall, slim man with boundless energy, looks very different from many other university chiefs of medicine in this country – and not only because, whenever possible, he travels by bike rather than driving a presti-

gious limousine. Of course, that alone says a lot about him. He is the only chief of medicine of a university hospital who is also employed as a Director at a Max Planck Institute, the Max Planck Institute for Heart and Lung Research in Bad Nauheim. When necessary, he thinks outside the box when it comes to science. He has crucially raised awareness about pulmonary disease – for decades a neglected problem – among the public and those who allocate research funding. He speaks often and in equal measure about luck and purpose when he talks about his career. “As doctors, we have a mandate to do everything possible to maintain the miracle of breathing freely,” he says. And yet, after more than 30 years of daily hospital life, it seems to an observer that, despite his huge success as a doctor and researcher, he still has not lost his concern for patients. These are people who are often anything but highly educated academics, with extremely serious health problems, at the threshold between life and death. >



Werner Seeger and his limousine: Suitable for all weather and good for the lungs.









» Each patient must feel that they are treated as an individual, taken seriously and accepted.«

Nor is it any different this morning at 8:00 a.m. when we visit the general ward. At this time, he has already spent half an hour in the intensive care unit (ICU). He talks about two younger patients who are in an induced coma there as a result of the H1N1 swine flu virus. Their lungs are extremely damaged due to a massive acute infection, and they therefore had to be put on an artificial lung machine. "Their chances of survival are not very good, unfortunately," says the 57-year-old: "This is the reality in which I live." He says it as if he takes the powerlessness of modern

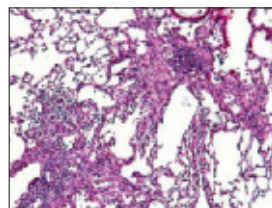
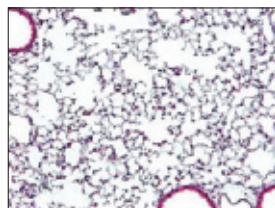
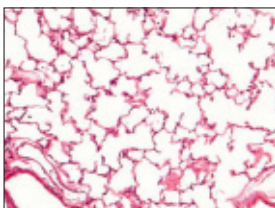
medicine in such situations personally, and the suffering of his fellow human beings as an incentive to keep going to alleviate the distress of patients with serious lung diseases. "At the end of my career, I would be happy to have it said about me that I contributed significantly to this," he says.

Extreme situations are part and parcel of life in the Giessen Lung Center, even in the general ward. Mr. L. has announced that he intends to end his life. He is serious. He suffers from a deadly pulmonary disease about which laypeople, even those who have

an interest in medicine, know very little: pulmonary fibrosis. His only chance was a lung transplant. After an agonizing one-year wait, doctors performed the transplant a few months ago and he initially responded well to the donor organ. Then he deteriorated again. The new organ is prone to constant infection and his lung function can't be stabilized. Now his bronchial tubes seem to be narrowing and he suffers increasingly from shortness of breath. His wife has left him.

Seeger takes a deep breath. This case has affected him personally. Nevertheless, he analyzes the patient's medical data calmly and objectively in the presence of the ward physicians and medical students. "The patient is considering a rational suicide," explains the doctor. The man is reflective, of sound mind and does not want a psychiatrist. The doctors can't force him to see a psychiatrist. "He's right. His situation is very serious," says Seeger, who nevertheless believes there is still a chance of stabilizing the donor organ with a different antibiotic treatment and by widening the narrowed

Lung tissue under the microscope: Smoking, inflammation or a genetic predisposition can destroy the pulmonary alveoli (center: healthy tissue). With pulmonary emphysema (left), the alveoli lose their elasticity, the inhaled air remains caught in the air sacs when the patient exhales. Excessive growth of connective tissue leads to pulmonary fibrosis (right).





Werner Seeger with a patient who is waiting for a lung transplant (left) and in the ICU of the new university hospital (right) with (left to right) Michael Barbrock, ward manager Alexander Pielka and nursing director Lothar Zörrb.

bronchial tubes using an endoscopic procedure. "This is what I will be proposing." On Saturday, after spending Friday in Paris, where leading experts are preparing the next world congress on pulmonary hypertension, he will speak to Mr. L. privately.

### FOCUS ON PATIENTS

Regardless of how difficult it may sometimes be, talking to patients is important to the professor. As he does his rounds, which last two hours today, he always adopts the right tone, makes a joke whenever possible, and delivers clear messages whenever necessary. He offers one patient, who is being treated as an in-patient for the 25th time in Giessen, a ticket for the opening ceremony of the new university hospital. He comforts another patient who is on the waiting list for a donor organ. The professor speaks clearly, in a language that people understand. "Each patient must feel that they are treated as an individual, taken seriously and accepted." This is how he describes his approach as a healthcare professional. "It is more

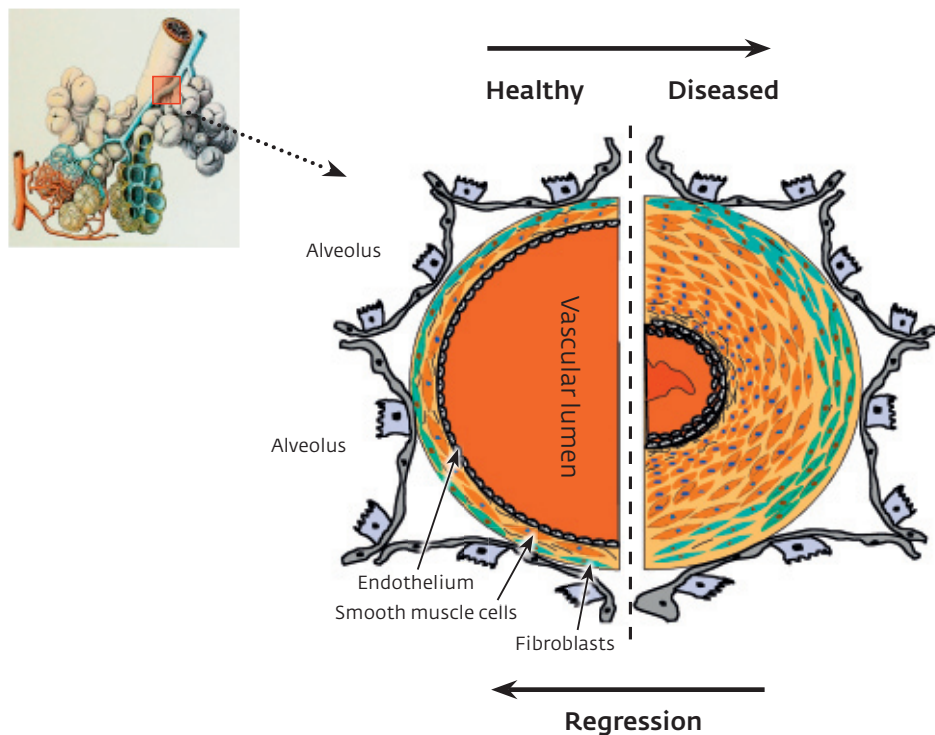
a question of basic attitude than the length of the conversation. When I speak with patients, I try to give them my complete attention." Seeger also endeavors to be a role model for younger doctors, which is extremely important: "This isn't something that you can learn in lectures, and certainly not in multiple choice tests." He knows that none of this is easy in the daily routine of a hospital: focusing on patients and at the same time protecting oneself from the daily suffering and the constant presence of death. "You really have to maintain a balance if you want to do your job well."

Seeing how he deals with patients would indicate that his past plays a role in this. Seeger comes "from a very modest background," as he puts it, growing up on a small farm in eastern Westphalia. When it came to choosing a career, becoming a teacher was the extent of his parents' imagination. This would have meant that he could also still work on the farm. But it was not to be. "I wanted a career that involved people," he says. Studying theology was thus one consideration for the devout Prot-

estant. Medicine was the other, ultimately more attractive, alternative, "because there I could do something more concrete, more practical for people." He was also seized with enthusiasm for research, a passion that he still retains today.

10:00 a.m.: The professor switches to his second world – science. Compared to his medical rounds, this is a radical change to a world of highly academic ideas and conversations, a micro- and nano-world of cells and molecules and intense debate, conducted in English of course, with doctoral students and young biomedical scientists from all over the world. "I feel lucky to be able to work in both of these worlds and to bring them together," he says. It is mainly thanks to Werner Seeger that Giessen currently enjoys an excellent reputation in pulmonary disease research. Worldwide. Up until the mid-1980s, however, pulmonary medicine tended to languish at the University Hospital of Giessen. Then the breakthrough came: with a clinical research group from the German Research Foundation (DFG) and a professor for "respi-





With pulmonary hypertension, several processes get out of hand. The cells in the blood vessel walls multiply excessively, narrowing the blood vessels. Tension in the blood vessels is also too high. Moreover, these contract due to a lack of oxygen. The pressure in the blood vessels then rises, making it increasingly difficult for the heart to pump blood through the lungs.

ratory failure.” Heading up this team was Werner Seeger, who was ultimately appointed professor of internal medicine in the mid-1990s, shifting the hospital’s focus to pulmonary disease. Giessen’s ascent in the area of pulmonary medicine peaked temporarily in 2006 with the establishment of the “Cardio-pulmonary System” Excellence Cluster, a joint venture with the cardiology department at the University of Frankfurt/Main and the Max Planck Institute in Bad Nauheim.

## FROM ROUNDS TO RESEARCH

Now the researchers from the cluster are meeting at a mini-symposium, as always to discuss their latest findings. The atmosphere is focused, yet relaxed. There is a lot of laughter. They all have respect for their boss, but are not afraid of him. The theme of the highly specialized lecture: the integrin signaling pathway in pulmonary hypertension. The spokesperson for the excellence cluster interrupts frequently, asks critical questions, looks at the data from all sides, and makes sugges-

tions. Brains are racked. His tone is positive and measured. The ambitious young scientists may want to impress with the necessary detailed knowledge, but Seeger, with decades of experience in many areas, is often the only one who is able to understand the findings in such a way that the team makes progress. “The different areas complement one another wonderfully,” he says, frankly admitting that, without the symposiums, he would lose touch with emerging technology and the latest findings in molecular biology. “I benefit enormously from them.” Ultimately, he is concerned with understanding what happens at the molecular level when pulmonary diseases develop, and which of the signaling paths involved can be tackled using active agents.

Up until a few years ago, for example, transplantation of a donor organ was the only treatment available for pulmonary hypertension. At a global level, 100 million people suffer from some form of the condition. In their pulmonary hypertension outpatient clinic – the largest of its kind in the

world – the Giessen-based experts frequently treat young women with the condition, often after pregnancy, “many of whom I have seen die under my care,” says Seeger. That is something that is not easy to shrug off. This is not the only reason why the team in Giessen has been plowing a large amount of resources into researching this disease since the 1980s.

Pulmonary hypertension is a disease of the lungs’ blood vessel system. In this pulmonary circulation system, as it is known, carbon-dioxide-rich, oxygen-depleted blood leaves the right side of the heart and enters the pulmonary arteries. The arteries divide into pulmonary air sacs (alveoli), where the blood is enriched with oxygen, and the carbon dioxide generated in the body is released. The oxygenated blood flows back to the left side of the heart, from where it is pumped around the body. In the case of pulmonary hypertension, the blood pressure in the blood vessels of the pulmonary circulation system increases, sometimes without any discernible cause, frequently as a result of other illnesses. The vessel walls thicken-



» A team player through and through: Some impress with detailed knowledge, Werner Seeger impresses with experience.

en, “mushroom” inward, and the lumen for the blood flow shrinks. As a result, the right side of the heart has to work harder and harder to pump the blood through the lungs and increasingly decompensates. This poses the threat of heart failure.

Under the aegis of Werner Seeger, the turning point in the treatment of pulmonary hypertension came after decades of stagnation. “Here at the Lung Center in Giessen, we have brought three drugs from basic research to worldwide approval,” says the researcher and doctor proudly: “That is more luck than a scientist can expect to have.” And the 57-year-old is a team player through and through. He immediately points out that it was primarily his colleagues Friedrich Grimminger and Ardeschir Ghofrani who discovered a treatment for pulmonary hypertension based on the impotence drug Viagra. In cell and animal experiments in the laboratory, researchers at the Lung Center had proved the significance of the molecule phosphodiesterase-5 in pulmonary hypertension. At the same time, the pharmaceutical in-

dustry had launched Viagra as a treatment for erectile dysfunction. The drug contains an active agent that inhibits phosphodiesterase-5. “It seemed logical to us that Viagra would also have to dilate the narrowed pulmonary vessels, which subsequently proved to be the case in animal experiments.”

#### NEW APPLICATION FOR VIAGRA

The researchers in Giessen embarked on an extraordinary study to prove that the same happened with people. At heights of about 16,500 feet and above, everyone suffers from pulmonary hypertension, which returns to normal once the person comes back to lower ground. So the doctors sent a group of mountain climbers and a suitably complex medical measuring device to Base Camp at Mount Everest. By yak! After a few days, they determined the expected high lung pressures of the test subjects, which also increased further under stress, and in this study proved the effectiveness of Viagra in reducing pulmonary hypertension in humans. The active agent was officially

approved in 2006 following an international, multi-center study initiated by the Giessen Lung Center on people with severe pulmonary hypertension. It has since been approved worldwide. Seeger and his colleagues had already been treating critically ill patients “off-label” with Viagra for years – always following tough discussions with the health insurance companies.

The most recent victory in this series of successful drug developments for treating pulmonary hypertension is the aerosol application of Treprostinil. The Giessen Lung Center in Bad Nauheim also provided the research basis for the active agents Riociguat and Imatinib, which are currently being tested in major clinical studies. Riociguat stimulates an enzyme, soluble guanylate cyclase, that plays a role in regulating stress in pulmonary vessels, as well as in regulating growth. Imatinib is already used in cancer treatments and inhibits a growth factor known as PDGF for short. It is a factor in the aggressive growth of tumors, but also in the “pseudo-malignant proliferation of the pulmonary



» Our goal must be to cure pulmonary hypertension, nothing less will do.«

vessels, which closes the lumen,” as Seeger says. Several active agents are now available. More are expected soon – the more, the merrier. This means that many patients can live more than 20 years with their condition.

### PULMONARY HYPERTENSION CAN BE CURED – BUT HOW?

“Undoubtedly a revolution,” says the Max Planck researcher, who seems only partly satisfied. “Our goal must be to cure pulmonary hypertension, nothing less will do.” After all, there is at least some proof that the phenomenon of “pseudo-malignant proliferation” of the pulmonary vessels is reversible. Reverse remodeling – reversing the pathological process to a normal vessel structure – is the concept that fires the researcher’s imagination. “Experimentally, we are making progress,” explains Seeger. In other words, the scientists are

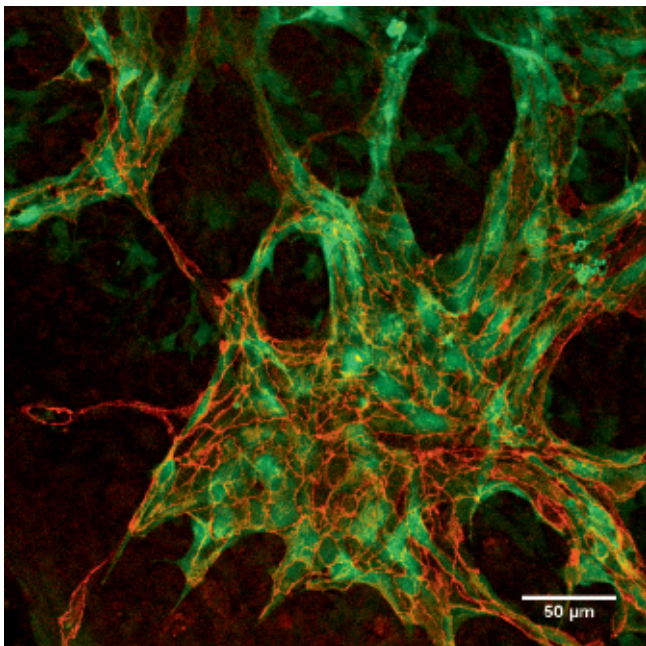
working hard to find substances and other ways of specifically influencing the signaling paths that control growth in the vessel walls of the lungs and thicken them.

Seeger has similar goals when it comes to researching pulmonary fibrosis. Some 750,000 people suffer from this disease in the EU alone. Of those, 400,000 suffer from the usually aggressive, rapidly progressing, idiopathic form. Its molecular basis is still widely unknown compared to that of pulmonary hypertension. With pulmonary fibrosis, excessive connective and scar tissue forms, destroying the architecture of the alveoli. The lung can dilate less and less and its function deteriorates, with the result that, at some point, the gas exchange no longer functions. Those affected find it difficult to breathe and are constantly prone to new infections and asphyxia. In the final stages of the illness, even speaking is difficult.

In Giessen and Bad Nauheim, researchers are examining what drives the pathological process. Among other things, growth factors such as TGF-beta and FGF-10 play a critical role. Werner Seeger doesn’t yet want to talk about a breakthrough with the first long-awaited effective treatment against idiopathic pulmonary fibrosis, nor about ARDS, the serious lung failure case requiring mechanical ventilation in ICU. No less challenging is the research of the chronically obstructive pulmonary disease of emphysema, in which the small pulmonary alveoli are gradually destroyed. Using stem cells, the researchers are trying to regenerate the lost tissue.

And, in fact, mice that have one lung removed regenerate their pulmonary alveoli completely, in the same way that amphibians can generate a lost tail. Young people can also regenerate their alveoli to a certain extent, with recently discovered pulmonary stem cells probably driving the process. “We successfully stimulated this regeneration of lung tissue in mice in the lab, and it would be fantastic if we could replicate the process in our patients,” says the scientist, as he moves briskly from the excellence cluster meeting to his next appointment around midday. He rarely stops for a break during his long working day. His day is jam-packed, but he never appears stressed. “I try to stay relaxed,” he says. “Of course, I do feel stressed, but usually it is a positive kind of stress because I enjoy my work.”

His third role awaits him, that of medical executive director of the University Hospital in Giessen-Marburg. He visits the university hospital’s new building. “This is the biggest building that was ever built in Giessen,” says Seeger. “We are getting a brand new hospital with 1,200 beds.” It is due to open in four weeks. Thinking about it,



Cells in the interior blood vessel wall. The endothelial cells are marked by a green fluorescent protein. An antibody reveals an adhesion protein that appears only in endothelial cells. The cells are derived from embryonic stem cells and have been cultivated to become endothelial cells in the cell culture.



Werner Seeger and Robert Voswinckel examine lung tissue using a confocal laser scanning microscope.

however, makes even a laid-back character like Seeger slightly nervous. Hundreds of patients will have to be moved within a short space of time, including the artificial respiration patients from ICU, together with the machines that they are connected to. Just two weeks ago, cables were still hanging from the ceiling in the admissions area. But now, the large space already looks more inviting. Seeger breathes a sigh of relief and appears somehow delighted as he scrutinizes the modern, high-tech spaces in the future intensive care units. It is apparent that this is a dream come true for him. "Patient management is entirely electronic," he gushes, instructing staff to perform a detailed function test on every single workstation before start-up. "Nothing dare go wrong, nothing," he mutters almost imploringly to himself.

1:00 p.m.: Patients are waiting in the outpatient clinic in the lung hospital. Seeger returns to his role of doctor. He doesn't need to wear the sym-

bolic white coat to radiate authority, a short-sleeved shirt will do. Despite his triple workload, he doesn't forget to eat. A salad – "healthy nutrition and exercise are important," he says and relates how, together with his wife, he has been involved for a long time in the German equivalent of Sunday school in his area, occasionally delivering a sermon in the Protestant university parish. His family, including his three children and four grandchildren, is central to his life: "I couldn't do my job without them."

#### FROM THE HOSPITAL TO THE RESEARCH INSTITUTE

3:00 p.m.: Following another appointment in the hospital's administration office, Seeger sets off for nearby Bad Nauheim. The second research focus of the day is pending in the Max Planck Institute. A colleague reports on his experiments using human induced pluripotent stem cells, or iPS cells for short, in

the manufacture of skin cells lining the interior of blood vessels. The goal is, at some stage, to use these cells in patients with pulmonary hypertension to induce the production of new "healthy" pulmonary vessels. However, the researchers first need to resolve a myriad of small problems that stand in the way of the ultimate goal. This is followed by a session in a small group designed to structure a research field that is still young: the investigation of the molecular mechanisms that encourage tumor growth in chronically inflamed lung tissue.

7:00 p.m.: Back to the hospital in Giessen, this time to his desk: e-mails, letters, loose ends and a few urgent phone calls. Finally, back to where the working day began, to a critically ill patient in ICU. Night has long since fallen on this March day when a man gets back on his bike and cycles through the fields of central Hesse. Fourteen hours as a doctor and researcher have come to an end. Until tomorrow at 7:00 a.m. ◀