Dr. Bernd Riedl – the chemist who discovered an anticancer substance

“Only happy researchers are good researchers”

Scientists who want to find an effective anticancer substance need plenty of stamina and usually a lot of luck as well as sound specialist knowledge. Dr. Bernd Riedl, a chemist at Bayer HealthCare, was responsible for synthesizing an active ingredient to treat renal cell carcinoma. This portrait takes a look at what motivates him, the conditions he needs to work successfully and how he recharges his batteries for his research work.

It sounds like something out of one of those fairytale success stories: a young man knows very early on that he wants to be a research scientist, experiences in his personal life lead him to the area where he will later work, and he goes on to develop a drug product for the treatment of an often fatal disease. Dr. Bernd Riedl is no fictional hero, however, but a real live researcher at Bayer HealthCare in Wuppertal. The 45-year-old's eyes sparkle and he gesticulates animatedly as he tells the story of his work to synthesize an anticancer active substance. The substance which he is credited with discovering belongs to a new class of cancer drugs called multikinase inhibitors. The compound is believed to attack cancer from two sides: it interrupts the signal pathway which stimulates the degenerate cancer cell to divide uncontrollably and allows the tumor to grow. It also literally "starves" the tumor by cutting off its blood supply. The active ingredient was jointly developed by Bayer HealthCare and the U.S. company Onyx Pharmaceuticals (see *research* 17).

Riedl knew the path he wanted to follow from an early age: he was the only one in his family in the town of Aalen in Swabia, Germany, to stay on at school and take the "Abitur" or school leaving examination. Up until year eight his progress "was very average". Then, suddenly, everything became clear: "After the first chemistry lesson, I knew what I wanted to do," recounts Riedl and laughs mischievously. Whilst he studied chemistry in nearby Stuttgart, he spent nearly every cent he had on motorcycling: "In summer we used to be out and about a lot and didn't study quite so hard," he remembers.

The fascination of complex natural molecules

Riedl only came upon organic chemistry quite late. "In Professor Ulrich Schmidt's group we cooked up complex natural molecules. I liked the fact that there was a practical purpose to what we were doing. We were trying not only to copy the complex systems which nature creates, but to outdo them too." Without the strong support of his parents, however, nothing would have come of all this. "They always encouraged me," says Riedl. And their encouragement paid off: today Riedl is one of the heads of the Chemical Research Department at the Research Center in Wuppertal and has just received the UCB Award for Excellence in Medicinal Chemistry from the European Federation of Medicinal Chemistry (EFMC) for the discovery of the anticancer substance.

Riedl was just 20 when his mother died. "After the diagnosis of cervical cancer, all we could do was watch," recalls the chemist. Then two close stu-

The happy scientist: Dr. Bernd Riedl (left) needs his motorbike as the counterweight to his research work. Riedl is now working with (left to right) Dr. Rudolf Schohe Loop and Dr. Susanne Röhrig on thrombosis research at Bayer HealthCare in Wuppertal.

Effective, unorthodox and successful: in recognition of his scientific achievements, Dr. Bernd Riedl and his team colleagues were awarded the Otto Bayer Medal in 2004 – the highest prize for scientific work at Bayer. Photo, center, left to right: Bayer CEO Werner Wenning, Dr. Bernd Riedl, Dr. Scott Wilhelm, Dr. Edward Huguenel, Dr. Udo Oels, then Bayer Management Board member responsible for Innovation, Technology and the Environment.

dent colleagues of his died - one within four months - of liver cancer. At that time he had no idea how this would spur him on to discover a novel active substance for the treatment of cancer: "It's not something you set out to do, it just weighs upon you somehow."

In 1992, armed with his doctorate in which he worked on a natural substance which was active against cancer in cell cultures, Riedl applied for jobs to a series of companies, including Bayer AG. For four years he carried out research, initially at the Bayer site in Wuppertal, into antibiotics with novel modes of action. Almost from the beginning, he was accompanied by his wife Martina, who had studied chemistry with him in Stuttgart. She worked in a school in Essen and trained medical technicians until the children came along. They soon agreed that she would stay at home and organize the whole family: "She not only manages the 'family firm'," explains Riedl, "she is the central figure who has everything under control and gets things rolling."

He relocated to the United States where he joined the ongoing Raf kinase project (see also *research* 15), in which the researchers were looking for compounds which switched off the crucial enzymes which play an important role in the division of tumor cells, as the chemistry project leader. Together with the biological project leader at the time, Dr. Barbara Hibner, he led the project team with about 25 colleagues from around the world which had been started by Dr. Hanno Wild and Dr. Timothy Lowinger. "You can only do it in a team. You can't go it alone," he says. "We all pulled together, sometimes in an unorthodox way, but very effectively. What matters is that you achieve your goal, not how you do it." In recognition of this team effort, he and his colleagues Dr. Timothy Lowinger, Dr. Scott Wilhelm and Dr. Edward Huguenel were awarded the Otto Bayer Medal in 2004 – the highest internal prize for scientific work at Bayer.

Before Riedl joined the project team, it had already spent a year screening all 200,000 compounds in Bayer's substance database at the time, and studying what effect they had on the enzyme Raf kinase. The team started working on a small molecule as a screening hit and synthesized closely related derivatives, which were then studied by the biologists. "What we had finally cooked up after the first year and a few learning cycles worked against cancer, but it was relatively poorly tolerated. We therefore wondered whether that was linked to the mechanism of action, the inhibition of Raf kinase, or was a pure coincidence," says Riedl, describing the researchers' dilemma. After another six months' work, they had the feeling that they were close to their goal. "We concocted a matrix of over 50 compounds and synthesized them all from A to Z. It was my firm belief that one of them was the right molecule." The team needed more than ten "learning cycles" until they were finally successful. "A small group of well-tolerated molecules was very effective against cancer, and one of them was the development candidate BAY 43-9006," says

Success in the States: whether working in the research and development team (left) or enjoying a private boating trip with colleagues (center), Bernd Riedl can look back on his time in the USA with pleasure. It was here that the Bayer scientist developed his anticancer substance in record time in collaboration with Onyx Pharmaceuticals. Riedl recharges his batteries for his current work in thrombosis research in the bosom of his family in Wuppertal (right).

Riedl. From this molecule emerged the active ingredient of today's anticancer drug. Dealing on a daily basis with the deadly disease has not weighed the young scientist down, however – he remains very positive.

Encouraging initial success with liver cancer patients

Back in Germany, the chemist found new areas of work in the Bayer HealthCare Research Center in Wuppertal but continued to follow the development of the active ingredient, through its extensive clinical testing as an observer. "It's like with your own child – you want to be there and you're pleased and proud when it continues to develop." It was particularly important to him to be involved in the negotiations for the first clinical phase at the tumor center in Essen. The tests dragged on at first. After eighteen months, however, Riedl saw the X-rays of a patient suffering from renal cancer with pulmonary metastasis. After two months' treatment, the metastases had virtually disappeared. What's more, in a patient with liver cancer there was a partial regression of the tumor. "It was an amazing feeling," says Riedl, beaming. "When I see the successes of the subsequent phases, I think of my fellow students who would have at least lived rather longer nowadays." Looking back on his conviction that a drug product capable of helping many people would be developed from this active substance, Riedl admits that he may have been rather naive. "But a good pharmaceutical researcher must have the firm resolve to find such a substance and then to develop it further," says Riedl. With this, he would have achieved one of his main objectives: "To achieve something in the battle against cancer."

As the joint leader of thrombosis research in the laboratories of the Wuppertal Institute, Riedl's dynamism and far-sightedness will continue to be much in demand in the future. "It's no nine-to-five job," he says. His own work is no longer the sole focus, however. "It's great fun leading groups, passing on experiences and motivating others," says Riedl.

The many nationalities at the institute and the collaborations with chemists, physicians and biologists make an open attitude essential. In addition, a research project's prospects for success are much greater when the interpersonal chemistry is right. "Individuals have to connect with each other, then the teams function properly and give each other constant encouragement. A great deal of self-motivation is required in research," he explains, and is convinced that "only happy researchers are good researchers."

The power source for his research work is his family, says the father of three, watching with a smile as his youngest, two-and-a-half-year-old Wilhelm runs through the living room. High-pitched children's voices come from the adjoining room where Caroline and Paul, the two older kids, are talking to their mother in the kitchen. Riedl's own four walls are filled with life. "I need my family as the counterpart to work. Everybody needs something to balance it out." In his youth it was the long evenings with his motorcycling buddies, today it is his family. The five motorcycles are kept in the cellar now. Now and again he tinkers with them and one of the children is allowed to go for a spin with him through the Bergisches Land area of Germany where he lives. All in all, a very down-to-earth family – and a long way from being a fairytale hero.

www.cancer.gov
This website (U.S. National Institutes of Health) offers detailed information on different cancers.