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HOW TO WIN THE NOBEL PRIZE

Nine tips from Peter Doherty* who won the Nobel Prize for Medicine in 1996, with comments by Harald zur Hausenn

TIP 1: BE REALISTIC AND DON'T OVERRATE YOURSELF

Harald zur Hausen: You have to be able to assess yourself realistically. Which after all is the mark of a good scientist. Never assume you know everything. And above all, don't act like a know-it-all

TIP 2: BELIEVE ONLY WHAT YOU SEE
AND TRY TO GET INTO THE HABIT OF
THINKING UNCONVENTIONALLY

Harald zur Hausen: I've often told young scientists how important it is to think outside the box once in a while. Simply contenting yourself with existing dogmas is both wrong and lazy. You don't have to accept everything you're taught, even if it counts as a scientific 'truth.' But if you take this approach, you must also expect to have to work harder.

TIP 3: WORK WITH THE RIGHT PEOPLE

Harald zur Hausen: Working in an environment that offers the right balance of freedom and direction is extremely important for young scientists, for whom too much freedom and too little direction can be disastrous. That's what happened to me at the start of my career. Later, when you've built up your own team, you have to develop a nose for talent. In my view, what helps here more than anything else is personal contact.

TIP 4: WRITE CLEARLY AND PRECISELY

Harald zur Hausen: One thing we have to be clear about: If the other person doesn't understand what I'm saying, then assuming he or she is of average intelligence it has to be my fault and not that of the person I'm addressing. Communication failures of this kind usually indicate that you haven't yet thought things through to their logical conclusion.

TIP 5: FOCUS ON A SPECIAL AREA; DON'T FRITTER AWAY YOUR ENERGY

Harald zur Hausen: Lack of focus is a real danger. Brilliant people who jump from one topic to another often achieve very little. You have to be obstinate, because no problem is easy to solve.

TIP 6: CHOOSE YOUR PLACE OF WORK

Harald zur Hausen: That's right. I've not always done that.

TIP 7: TALK ABOUT YOUR TOPIC

Harald zur Hausen: Those who brood over their problems all on their own and conduct wonderful experiments that no one ever hears about never get noticed and are soon forgotten. Surely the opposite is the more natural way: If you have some measure of scientific ambition, you'll most likely want to share what you're doing with your colleagues and if you're astute as well, then you'll want to hear their criticisms and suggestions.

BE TENACIOUS AND DOGGED, BUT ALSO BE PREPARED TO FAIL

Harald zur Hausen: Basically, you have to accept that most of the hypotheses that you advance and that you spend years of your life working on and tweaking will eventually turn out to be wrong. You then have to correct them – and go on working. You have to be prepared for a certain amount of frustration – perhaps even more so in science than in other areas. And no doubt about it, you also need luck. With the papillomaviruses, I was lucky.

TIP 9: STEER CLEAR OF PRESTIGIOUS MANAGEMENT JOBS

Harald zur Hausen: Assuming it really is a job in which you're no more than an administrator, then I wholly subscribe to this statement.

"THE PRIZE IS A CREDIT TO US ALL"

The Nobel Prize – an honor and a challenge for the DKFZ



Monday morning, October 6, 2008: Harald zur Hausen is editing an article for the International Journal of Cancer in his office in the Applied Tumor Virology building. In the neighboring main building the Administrative-Commercial Director Josef Puchta is studying plans for the Center's new buildings and renovations. The Scientific Director Otmar D. Wiestler is on a plane to Berlin, where he is to give a lecture. At a quarter to eleven zur Hausen's phone rings. "I picked up the phone," he says, "and heard a voice with a Swedish accent congratulating me on winning the Nobel Prize." From then on chaos reigned supreme. "All hell broke loose," recalls the new Nobel Laureate - who is not normally one to exaggerate.

"No, we really hadn't been expecting it," says Wiestler, explaining why the current head of the German Cancer Research Center (DKFZ) only learned the good news when he landed in Berlin and switched his cell phone back on again. From then on, he recounts, his sole concern was to get back to Heidelberg as quickly as possible: "This was obviously going to be the high point of the year."

In Wiestler's opinion, there is hardly any research scientist in biomedicine who has achieved what his predecessor Harald zur Hausen can show for a life's work. To shape the entire development from the first bold hypothesis right up to the finished product – the vaccine against cervical cancer now available in every pharmacy – was "something really, really special."

Otmar D. Wiestler succeeded Harald zur Hausen as Scientific Director of the DKFZ in 2004. "The German Cancer Research Center is an outstanding institution," he says, as he himself realized soon after taking office. "And what makes it so outstanding are the people – a truly remarkable number of excellent brains at all levels of the organization." In his travels in Germany and abroad, he has time and again been witness to the high esteem in which the German Cancer Research Center is held. And now the Center is famous as well. People will say: "The DKFZ – they're the ones with the Nobel Prize Winner." As Wiestler remarks: "It's a wonderful award for Harald zur Hausen. And a wonderful award for the DKFZ, too. The prize is a credit to us all." And an honor the DKFZ must continue to live up to.

"We have a special tradition and a special responsibility," says Wiestler. The responsibility addresses first and foremost people who have cancer. Cancer diagnosis and therapy have improved considerably, but the fact is that one in two cancer patients still cannot be treated successfully and eventually succumb to the disease. "We are in urgent need of new therapies," explains Wiestler, who regards being part of this effort as one of the DKFZ's most important tasks. The prospects for success are certainly promising. In the

past 20 years, research has laid the groundwork for therapeutic innovations at the cellular and molecular levels in particular. "Using this excellent basic research as a springboard," says Wiestler, "we now have to focus more on applied medicine. After all, taxpayers support us so that we can do something to combat cancer."

"Translational cancer research" is the term used for research that aims to get its findings out of the laboratory and into the hospital as quickly as possible. The clinical cooperation units initiated by Harald zur Hausen in the early 1990s are a step in this direction since they help bridge the gap between research and clinical practice; one clinician is placed in charge of both a DKFZ research unit and a hospital ward. Then, in 2004, the National Center for Tumor Diseases Heidelberg (NCT) was founded, and will move into its new building at the beginning of 2010. Modeled on the American Comprehensive Cancer Center, the new NCT complex will bring together cancer researchers and cancer specialists to care for patients under one roof. Rapid translation of research findings into practice, says Wiestler, also requires close cooperation with partners from



Prof. Dr. Otmar D. Wiestler, Chairman and Scientific Director of the German Cancer Research Center



The Applied Tumor Virology building where Harald zur Hausen can be found in his office almost every day

industry. The DKFZ has therefore formed strategic alliances with partners such as Siemens in medical technology and Bayer Schering Pharma in drug development.

Another important goal, according to Wiestler, is the improvement of early detection and prevention. "The earlier cancer is detected," says Wiestler, who is himself a physician, "the better the chances of a cure." Greater emphasis is therefore being placed on research into prevention and risk factors to stop cancer from developing in the first place. Vaccination against cervical cancer is a unique example of this. The new Preventive Oncology unit at the NCT reflects the importance of this area.

Not that basic research should be neglected, says Wiestler, who is anxious to stress the importance of its role as the

foundation for all future clinical developments. Basic research in cell biology is receiving special attention thanks to the alliance with the DKFZ's neighbor, the Center for Molecular Biology Heidelberg. Wiestler also underscores the importance of programs to nurture young scientists. The Theodor Boveri Program for the advancement of young scientists, for example, was created by Harald zur Hausen himself to give them the opportunity to work independently and establish their own research groups early on (see pages 18-21). The DKFZ now has twenty such junior research groups. "The institution has an outstanding reputation," says Wiestler, adding that "excellent young scientists are eager to work here - and we do all we can to offer them the very best condi-

The new NCT building is due to be completed by the end of 2009.

tions."



The National Center for Tumor Diseases aims to get research results to patients as quickly as possible.

Wiestler also mentions a new research focus – newly discovered cancer stem cells. The Heidelberg Institute for Stem Cell Technology and Experimental Medicine (HI-STEM) was founded just recently to conduct stem cell research at the highest international level and to develop cancer therapies in close cooperation with hospitals and industry.

Another new focus will be participation in the international Cancer Genome Project. The aim of this mammoth undertaking is to analyze the entire genome sequence of the 50 most common cancer types in 500 patients each in order to detect frequent genetic mutations in cancer cells. This is a precondition for developing new medicines and for individualized cancer care. 'Admission' to the project costs 15 million Euros. "That's a lot of money," says Wiestler, "and we had to

fight for months to win support for a German contribution." Yet he has no doubt that it is a worthwhile investment, and that as a trendsetter for cancer research and cancer medicine, it will soon start yielding dividends for both the diagnosis and treatment of cancer.

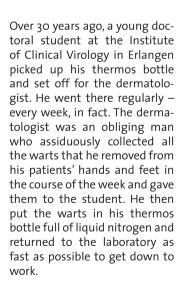






THE LONG ROAD TO SUCCESS

From an interesting discovery to the first cancer vaccine



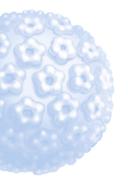
The young PhD student was Lutz Gissmann. Now a professor and head of the Genome Modifications and Carcinogenesis division at the German Cancer Research Center, Gissmann recalls how "there were ever so many warts." His supervisor had tasked him with searching for the DNA of particular viruses, so-called papillomaviruses, in genital tract warts. The supervisor was Harald zur Hausen, who when he arrived in Erlangen was just 35 years old, and had advanced the remarkable hypothesis that papillomaviruses cause cervical cancer. All that he lacked was proof.

Gissmann worked systematically, starting with the hand and foot warts on which the research was more advanced. Zur Hausen had isolated papilomavirus DNA back in the early 1970s and had demonstrated that the viral DNA obtained from hand and foot warts was different from that obtained from warts of the genital tract.

Both are benign growths of the skin, but are caused by different types of papillomavirus, or so zur Hausen hypothesized. The question called for in-depth study, and Gissmann was one of the first PhD students to work on human papillomaviruses (HPV) in zur Hausen's Erlangen team.

Lutz Gissmann recounts how he first heard the name Harald zur Hausen in a lecture on tumor virology he attended while a student at Erlangen in the early 1970s. A short time later, he learned that zur Hausen was to leave Würzburg to take up an appointment at the Institute of Clinical Virology at the University of Erlangen-Nuremberg and immediately decided: "That's where I want to be." He later buttonholed zur Hausen in the corridor of the Institute and without further ado after introducing himself briefly asked whether zur Hausen would supervise his doctoral thesis. The response was similarly short and to the point: "So when do you want to come?"

Gissmann, however, first had to complete his diploma in Biology, although "I'd often wander over to the Institute of Virology





just to show him that I was still around." He was afraid his future supervisor might no longer remember him, although zur Hausen was quick to reassure him on this point: "I'm waiting for you," he would say.

Lutz Gissmann set off with his first thermos bottle in the mid-1970s. The laboratory work on the warts was highly complex and called for all the methodological tools of the trade then known to molecular biology in those days a relatively new branch of science. The findings, however, were crystal clear: Warts on hands and feet were indeed found to be caused by different types of papillomavirus than those on the genitals. This was a very important that corroborated finding Harald zur Hausen's hypothesis. Whereas skin warts on the hands and feet are always harmless, genital warts - as had been known for some time - in rare cases can degenerate into cancer. Was it possible that the papillomaviruses which showed such a clear preference for cervical tissue were at the same time the pathogens that caused cervical cancer? And if so, which types of papillomavirus were involved? Meanwhile,

scientists had discovered that there are numerous different types of papillomavirus, most of which are harmless. The next scientific task, therefore, was to track down the culprits.

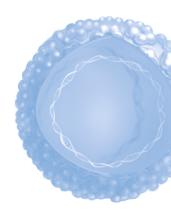
1977 saw a change of scenery. Harald zur Hausen had been appointed Professor at the Institute of Virology at the University of Freiburg and many members of his group, Gissmann among them, decided to move with him. They were joined by the PhD students Michael Boshart, Matthias Dürst, and Hans Ikenberg. The wart era was also over. The objective now was to isolate the DNA of papillomaviruses in tissue samples taken from cervical tumors that had been surgically removed from women patients. Until then, this had invariably proved impossible; but now, modern genetic engineering held out the promise of success.

And success was not long in coming. Between 1982 and 1984, Harald zur Hausen's team isolated the DNA of two types of papillomavirus from cervical tumors: HPV16 and HPV18. These two papillomaviruses are known to cause about 70 percent of all cervical tumors and precancerous lesions.

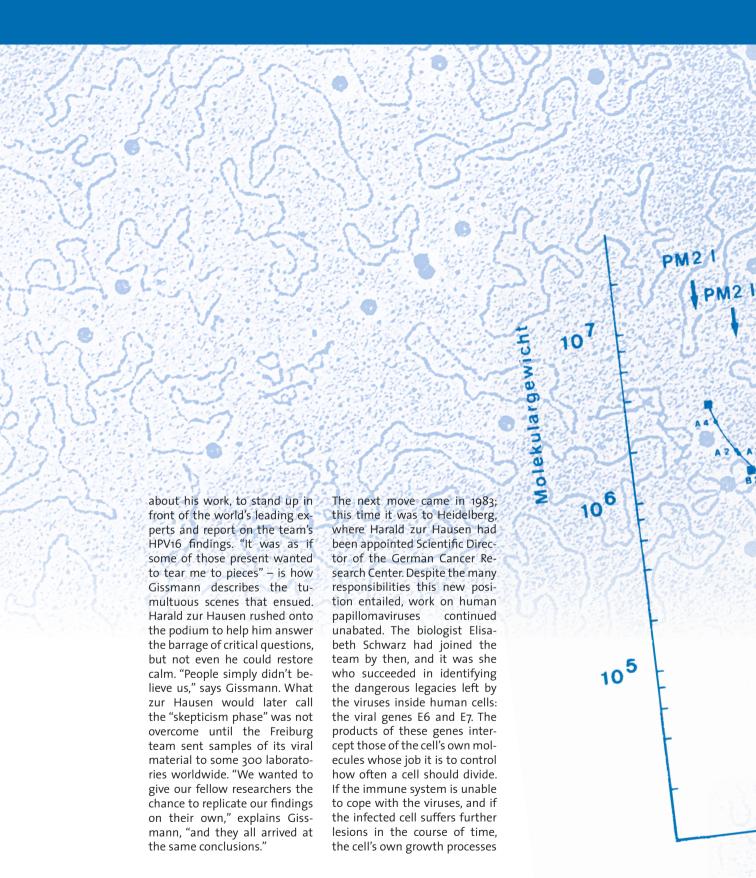
Gissmann recalls how "we even discovered HPV18 in HeLa cells." HeLa cells are descendants of cells obtained from cervical cancer tissue taken from Henrietta Lacks, an American woman who died of the disease in 1951. Since then, the cancer cells, which continue to divide, have been

used by institutes worldwide for biochemical and molecular biological research. Even today, says Gissmann, he is impressed that papillomavirus DNA can be detected in a cell line that has existed for decades: "Those were real breakthroughs in Freiburg."

Yet the scientific world outside Freiburg's Institute of Virology still had to be convinced. Lutz Gissmann recalls an event in the mid-1980s which apparently does not count among "the greatest experiences" of his life. He was in Sweden for the annual conference of papillomavirus researchers and it fell to him, a young scientist lacking in experience, but very excited







– finely balanced at the molecular level – may be upset, leading to unbridled cell proliferation at the expense of healthy cells. This explained the apparent 'transformation' of infected cervical cells into cancer cells, often decades later. And the scientists had another idea, too: If viruses are the main cause of cervical cancer. cology before pouring money into an illusory cancer vaccine. "The link between viruses and cancer did not generate much enthusiasm on the whole," says zur Hausen, "and the idea of vaccinating against cancer probably seemed too remote." One German pharmaceutical company that he had been able to take on board backed out after the results of a market analysis suggested that the development of a vaccine would not pay off.

form virus-like particles, which outwardly resemble the natural viruses, but do not contain any DNA and are therefore not infectious. These particles became the basis of the vaccine which has been available since 2006 and which in large-scale clinical trials has been shown to provide reliable protection against infection with the human papillomaviruses 16 and 18 and hence precancerous cervical lesions. "So we've now come full circle," says a delighted Gissmann.

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why should it not be possible to develop one of medicine's most powerful weapons – a vaccine – against this form of cancer? The idea was good, but no one was interested in it. Various industrial partners were approached, but none of them was willing to provide the financial backing for such an expensive long-term undertaking. "Some of them thought the experimental data were insufficient,"

There

were problems in the lab as well. The papillomaviruses simply refused to be cultured in the Petri dish. Yet such cultures are essential to obtaining the harmless viruses required in a vaccine. The breakthrough came in the early 1990s, when Lutz Gissmann and Matthias Dürst, along with scientists from the US National Institutes of

The

full story of the importance of viruses and other pathogens to the pathogenesis of cancer in humans has yet to be written, however. "I'm absolutely convinced," says Harald zur Hausen, "that infectious events

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recalls Harald zur Hausen. Others told him that surely there were more urgent problems that needed tackling in on-

0.8

Health, used genetic engineering to produce large quantities of one of the virus capsule's protein components. These components combine spontaneously to

1.0

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play a much greater role in the development of cancer than has hitherto been assumed. And it would make me very happy if I could encourage young scientists to follow up this lead."

1.6

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"KNOWLEDGE IS MORE

Harald zur Hausen – a portrait









Harald zur Hausen cherishes the hope that one day we will be able to overcome cancer, though he would never dare make such an assertion in public. What he would say is that we are learning to understand it better. And he is confident that this increases our chances of taking the sting out of cancer, or even of preventing it from developing at all. Cancer prevention, stopping cancer from developing - the work of Harald zur Hausen is a textbook example that this is possible. Thanks to his seminal research, medical science has developed the very first vaccine to target a specific type of cancer, cervical cancer. A member of the Nobel Prize Committee praised the "great perseverance" with which Harald zur Hausen pressed ahead with his research over the decades, even in the face of opposition. "The bit about perseverance is certainly true," says zur Hausen, "I'm as obstinate as a mule."

Harald zur Hausen was born in Gelsenkirchen on March 11, 1936. His schooling began when he was six, but ended almost as soon as it had begun. The war was on, and the school had to close, which "wasn't such a problem for us children," zur Hausen recalls. When schools opened again in 1945, his aunt, a schoolteacher, made sure her nephew could go directly into fourth grade. "I was completely lacking in fundamentals," zur Hausen says. But he still passed the exams he needed to advance to the next level – probably in the early summer of 1946: "I've no idea how I managed it - very likely by the skin of my teeth."

IMPORTANT TO ME THAN POWER"

The first year at Gymnasium (high school) was "simply terrible," and his report card at the end of the year read: "Passed but with great misgivings." He describes how he then boned up on what he was lacking and how from then on, things went pretty well: "I'd say I was an average student." What was unusual, though, was his enthusiasm for nature. Even as a small child he took a keen interest in plants and animals, especially birds, and even enjoyed gardening! He and a friend of his who lived on a farm would often venture off into the nearby forests and heaths, where they would "collect all sorts of things or catch lizards – the kind of things boys do." Even later after he and his family had moved away from the Ruhr Area to Vechta, south of Oldenburg, he liked to spend hours, usually alone, walking on the moors and observing the natural world. His exceptionally deep and precocious affinity for nature and for all living things was "probably a little on the unusual side" – or so Harald zur Hausen thinks in retrospect.

He may have inherited this early interest in flora and fauna from his father, who came from farming stock near Gladbeck and had had to break off his study of agronomy because of the First World War. In 1919, he ended up as a soldier with the Baltische Landeswehr in Latvia "which is where he met my Latvian mother," recounts zur Hausen. "They got married four weeks after meeting, and surprisingly, their marriage lasted a lifetime." Like so many people in those days, his mother did not have an easy life. Her father had died

of tuberculosis when she was a young girl and shortly afterwards she lost her mother – "to cervical cancer, incidentally."

Zur Hausen remembers that his mother had always said she would have liked to become a doctor. "But in the difficult war and post-war years, she had no opportunity to realize this wish," he says, adding that perhaps his interest in medicine came from her. His mother was always happiest when she had all her children with her. There were three sons and a daughter, and Harald was her youngest child. "We didn't have it easy financially," says zur Hausen, "but we did all get a good education."

Once at Gymnasium, his keen interest in the natural sciences quickly became apparent. Biology was his favorite subject. and he was "fairly ambitious" in it. He liked Chemistry, too, and also enjoyed writing, especially the essays on literature and philosophy he had to write for German in his last year of school. In his free time, he liked to read the biographies of famous scientists, and was particularly impressed by the life of Robert Koch. The subject he relished least was Religion, nor did he much care for his Religious Education teachers. "I got into really heated discussions with them," recalls zur Hausen. Even as a schoolboy, he was fascinated by "the central and burning issue," convinced as he was that it must be possible to find a mechanistic explanation for all life processes. The contradiction between what he learned in Religious Education and his experience in the natural sciences

was, he believes, a challenge that shaped his thinking. Even today the auestion continues to engross him, and two years before he retired as Scientific Director of the German Cancer Research Center he wrote a book called Genom und Glaube or "Genome and Belief." His main thesis in that work is that belief should be replaced "by knowledge wherever possible" and "mental stasis" by the dynamic thinking prescribed by evolution. "Of course we do not know whether this rational approach can assure our future," he writes in his final sentence, "but do we have an alternative?"

After graduating from high school in 1955, zur Hausen opted for a two-in-one solution and began studying Biology and Medicine at the same time. Amazingly, he held out for seven semes-



ams, my decision very nearly turned into disaster because I simply didn't have the time to attend any lectures in Medicine." He therefore had to work "as never before and as I never have done since" to catch up on what he had missed. The decision to give up Biology was also influenced by the fact that teaching at Germany's universities "was simply poor back then." There were hardly any lectures in Molecular Biology, for example, although it was already becoming a mainstream subject by then. Instead, he was expected to draw insect mandi-



1967 in Philadelphia

bles. Not that there is anything wrong with that—there is a place for everything. But this approach meant that too many developments passed him by, which as a young scientist he then had to learn about by dint of very hard work after graduation.

After passing his preliminary exams with flying colors, everything went smoothly, even if his first doctoral thesis at the Institute for Tropical Medicine in Hamburg turned out to be a dead end: "I was supposed to count amebic cysts in the stools of monkeys," zur Hausen recalls.

When he calculated that this mindless task would take at least three years, he lost all interest and switched to the Institute of Microbiology in Düsseldorf, where he addressed a topic that at first glance seemed to have nothing at all to do with either Biology or Medicine. He studied floor waxes! Initially, he admits, he found this research extremely uninspiring; but he kept at it and in the end found it very interesting. Because what zur Hausen found out was that when exposed to ultraviolet light, certain floor waxes used in tuberculosis sanatoria kill Mycobacterium tuberculosis,

the very bacterium that causes tuberculosis. "So, I'm not in the least ashamed of my PhD thesis," he says.

After completing his doctorate, Harald zur Hausen spent the years 1960 to 1962 as a resident in hospitals in Wimbern (Sauerland), Isny (Allgäu), Gelsenkirchen, and Düsseldorf. "I wanted to get myself licensed as a medical practitioner," he says, "and that meant I had to do the clinical work." Those were two very good years in which close contact with patients affected the way he thought – and continued to do so even later, long continued on page 16

Floor waxes played a central role in zur Hausen's PhD thesis.

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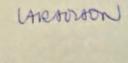


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Top: Harald zur Hausen (smoking!) with Heinrich Schulte-Holthausen at his graduation ceremony, New Year's Eve 1960.

Bottom: Award of his Doctor honoris causa by Prague University, 1994.

after he had found his place in research. "In my heart of hearts, I always wanted to do pure research," zur Hausen readily admits. But when he finally started his research career at the Institute of Hygiene and Microbiology at the University of Düsseldorf, he was deeply disappointed: "Those were the bleakest weeks of my life," he recalls. "There was no one to guide me and all I could do was stand around in the lab, helplessly asking myself: So what?"

His much-praised perseverance was so sorely tested that "I made up my mind to go back into clinical medicine." But a "chain of odd circumstances" prevented his return. After various unsuccessful attempts to find an attractive job, work in the Düsseldorf lab started to improve, "and I rediscovered my joy in doing research."

The years 1966 to 1969 were a crucial time. Harald zur Hausen spent them with Gertrude and Werner Henle, a research couple of German origin at the Children's Hospital of Philadelphia in the USA. The young zur Hausen came by this job in a most unusual way: He pulled it out of the wastebasket! Looking for a research assistant. the Henles had sent an inquiry to Düsseldorf; but because no one was interested, their letter had eventually been thrown away. "When I accidentally heard about the inquiry," says zur Hausen with a grin, "I went and fished the letter out of the wastebasket and applied." He insists that he owes much of his scientific craftsmanship to this fortuitous circumstance -

and to his first hands-on involvement in a topic that was to remain with him for the rest of his life as a research scientist. In the early 1960s, Gertrude and Werner Henle were the first to demonstrate that there is a connection between a specific virus, the Epstein-Barr virus, and a particular form of cancer, Burkitt's lymphoma, which occurs frequently in Africa. "Viruses and cancer" – that was to be zur Hausen's research topic.

The topic was peripheral, but very promising. The field had by and large been left fallow, and Harald zur Hausen wasted no time before applying himself to the job of tilling it. On leaving the United States, he went first to the University of Würzburg, where starting in 1969 he had the opportunity to build up his own research group at the Institute of Virology, and then, in 1972, to the Institute of Clinical Virology at the University of "Those Erlangen-Nuremberg. were happy years," he recalls.

In 1977, he was offered the post of Professor of Virology at the University of Freiburg and after much deliberation accepted it. "The Freiburg Institute of Virology was well established," zur Hausen recalls, "but had a relatively poor reputation owing to the public controversy surrounding professors' income from other sources. I considered it a challenge to take on the job." Almost his entire team from Erlangen went with him. It was in Freiburg that he amassed the fundamental findings which would later provide the basis for the development of the vaccine for cervical cancer. Otmar D.

Wiestler, current Chairman and Scientific Director of the German Cancer Research Center, was a young resident physician in Freiburg at the time and met Harald zur Hausen on a joint research project. "He was already someone for whom we had the highest esteem," Wiestler recalls, "and someone we were slightly in awe of."

The next challenge came in 1983 when the German Cancer Research Center in Heidelberg was in crisis and in urgent need of a new boss. Harald zur Hausen explains how given the endless difficulties he was having with the administration of Freiburg University and with its then Chancellor, he was not averse to the idea of a change. "I drafted a concept and was given an opportunity to present it to the Scientific Council of the DKFZ," he says. "I was asked a number of tough questions, including what made me think I could run an institution as large as the DKFZ."

As everyone will attest, he was soon running the DKFZ very well indeed - and continued doing so for twenty years from 1983 to 2003. During that period, the German Cancer Research Center in Heidelberg evolved into one of the world's leading cancer research institutions. Even his former critics were soon full of praise for zur Hausen as both scientist and science manager. Only zur Hausen himself secretly harbored doubts. "I won't try to hide it – I spent 20 years wondering whether the decision to leave Freiburg for Heidelberg was the right one." Despite all the problems that he had

had to cope with in Freiburg, he believes that in the end, he had more time there for intensive research. In Heidelberg, on the other hand, he was obliged to delegate much of the work that he would have preferred to tackle himself. But "as managing directors go, I think I was unusually active as a scientist," he says, "even if I still ask myself whether I didn't miss out on a number of opportunities."

"I've never felt the need to exercise power," says Harald zur Hausen; "power has never really excited me." What he did find exciting, though, was getting the chance, as Chairman and Scientific Director of a large institution, to influence the course research was taking and to bring about a change of direction. "I believe I can safely say that I missed few opportunities of bringing this influence to bear here at the DKFZ. That gave me great satisfaction. And I was even more satisfied when I saw that things really were running very well indeed."

And apart from science, what does Harald zur Hausen the man consider important? "You can't really separate the two," he replies, thoughtfully placing his large blue coffee cup with the initials HzH on a small table. "What has always been important to me personally," he reflects, "is to approach both people and things with a certain equanimity and friendliness. I hope I've succeeded in this in the main."



A GREAT NOSE FOR TALENT

A research center depends for its success on its "brilliant minds". Harald zur Hausen attracted many such minds to the DKFZ. Here are just a few.



BOUTROS

From Harvard Medical School to the DKFZ – how come?

In 2002, I had been a postdoc at Harvard for three years and was looking for a place where I could build up a junior research group. So the announcement of the Theodor Boveri groups at the DKFZ came at just the right moment.

But your special field was not in fact cancer research at all.

That's right. We were studying signal pathways in cells with a fairly new technology known as RNAi screens. Using RNA interference, we were able to suppress just about any gene in order to study loss of function. We were working exclusively with the Drosophila fruit fly, and there was no way of knowing whether our approach would work in human cells. But that of course was a precondition for using RNAi screening in cancer research.

But it seems you were still able to convince Harald zur Hausen of your idea?

Yes, he was immediately excited by the idea and ready to support our high-risk project.

And it paid off?

Absolutely. We actually succeeded in transferring the system to human cells and here found a number of new signal factors. One of our PhD students has just finished her thesis in which she examined whether these factors are regulated differently in tumor tissue, for instance. Work is also being done to determine whether signal factors play a role in the development of cancer. We're also planning the next step. We intend to study which factors in cancer cells are responsible for the frequently observed resistance to chemotherapeutics and, vice versa, which factors make the cancer cells particularly susceptible. Our goal is to be able to use this knowledge in therapy one day.

How has your area of research developed on the whole?

There's huge interest in it. Here at the German Cancer Research Center, we're offering courses on RNAi screening and always have one or two visitors in the lab who want to learn the method from us. Suppressing individual genes is of course interesting

for all kinds of problems, and we're cooperating with many groups both here at the Center and elsewhere, such as with colleagues from the MD Anderson Cancer Center in the USA.

What did October 6 mean for you?

What a day that was! The television crews, the hubbub and the excitement all over the DKFZ – it was better than winning the World Cup!

Professor Michael Boutros heads the Signaling and Functional Genomics division. He is interested in the signal factors that control cell replication and survival and therefore play a role in the origin of cancer. To find out which functions a gene has, scientists use a technique known as RNA interference. Boutros has received prizes for his work, including the Johann Georg Zimmermann Prize for Cancer Research, which in 2007 was awarded to both him and Harald zur Hausen jointly.



CFRWFNKA

Back in 2002, you had a wellpaid job with a pharmaceutical company in Vienna. Why did you nevertheless apply to the DKFZ?

At that time I wanted to get back into academic research. I had been a postdoctoral fellow in the USA for six years before that and had done some very successful research in the area of innate immunity. So, when I saw an ad in DIE ZEIT for junior group leaders at the DKFZ, I applied.

And you were invited to give a talk...

Yes, fortunately. There were 15 candidates and we all had to give a talk as well as being interviewed individually. That's when I met Harald zur Hausen for the first time and I remember thinking: "What a charming man!" The initial contact was very brief, but I was most impressed. Two days after returning to Vienna, I received an email offering me the job.

Was Harald zur Hausen just as charming when it came to ne*gotiating* your contract?

He most certainly was. The meetings always took place at eight o'clock in the morning. That was tough for me, because I was traveling from Vienna to Heidelberg by train. And when he greeted me on my arrival in the morning, he always asked: "Ms. Cerwenka, would you like

a coffee?" In the beginning, I made the mistake of saying "Yes," and then we talked about this and that and before I knew it the time was up and we hadn't really covered all the points. So after that, my strategy was always to say "No" when he offered me a coffee, if only to make sure we got through the agenda.

How has your research at the DKFZ developed?

Very positively. I've been able to continue working in my field, which is natural killer cells. I have a lot of freedom. I've been able to work absolutely independently, and with a great deal of help from the Center I soon succeeded in obtaining funding. My team has since grown from four to nine people and I've found a number of cooperation partners here at the Center. Together with Lutz Gissmann, for example, I'm investigating how natural killer cells react to cells infected by papillomavirus.

What about the field of innate immunity as a whole?

The field is booming, especially in vaccine research. In addition to the actual antigen against which an immune response is to be elicited, vaccines also contain so-called adjuvants. These are components that enhance the immune response, and they act via the innate immune system. Needless to say, these adjuvants play a role in the tumor vaccines being developed here at the DKFZ, where we're trying to provide a vaccine against the body's own cancer cells.

Dr Adelheid Cerwenka heads the Boveri junior research group "Innate Immunity." She has received a number of awards for her work, including the Marie Curie Excellence Grant and a Helmholtz Association Prize. awarded to her together with Michael Boutros.





LICHTER

Dr. Lichter, can you recall your first meeting with Harald zur Hausen?

Yes, of course. It was in 1989. I was a postdoc at Yale at the time and having developed an entirely new method of determining the position of individual genes on chromosomes had some terrific offers in the USA. However, I really wanted to come back to Germany and had written a slew of letters, but never received an answer. So I made a tour of Germany, in two weeks giving ten talks, one of which was at the DKFZ.

That was the time when the human genome project had just gotten off the ground, so your method was very timely.

In the USA, the human genome project was in full swing; in Germany, though, people were extremely skeptical about genome research. I addressed the problem directly in my discussion with Harald zur Hausen, telling him that I was meeting with rejection everywhere I went. "Well we have to do something about that!" he said, and that was when I knew that this was the right place for me.

How did the other scientists in the DKFZ react?

They were very skeptical, and there was some conflict; but in such matters Harald zur Hausen was just as insistent as he is in his own research. He wouldn't veer from the path he'd taken and stood by his decision, which meant he stood by me too.

And the decision proved to be the right one...

Cancer research can't do without genome research; after all, cancer is a disease of the genes. And quite apart from cancer research, the decision to introduce genomics at the DKFZ was visionary. With Annemarie Poustka and others, the DKFZ became the hub of genome research in Germany.

What has genome research done for patients?

By expanding our investigations to include the genome, we've been able to find a number of molecular changes in cancer cells. There are now drugs such as Glivec and various antibodies that target changed structures in cancer cells. We're now able to discern specific differences between tumors and decide which therapy has the best chance of success. And if the speed at which entire genomes

are being analyzed continues to increase, it's possible that every patient will soon have access to individualized treatment.

Do you still meet Harald zur Hausen occasionally?

We meet for lunch every Thursday at the editorial meetings of the International Journal of Cancer, of which he is the Editor-in-Chief.

Professor Peter Lichter heads the Molecular Genetics division. Among the awards he has won for his research work are the experimental part of the German Cancer Prize 2002 and the German Cancer Aid Prize 2003. On the retirement of Harald zur Hausen in May 2002, Peter Lichter became Acting Scientific Director of the DKFZ.



LYKO

How did you come to the DKFZ?

I was in a fortunate position back then. I had a five-year Emmy Noether Grant from the German Research Foundation (DFG) and after spending two years abroad with Rudolf Jaenisch at the Whitehead Institute in Cambridge, USA, wanted to come back to Germany. When I first applied to the DKFZ, I actually wrote to Ingrid Grummt, whom I had known previously. She no doubt supported my application, but of course I still had to meet the Scientific Director.

And how did the meeting with Harald zur Hausen go?

First of all, the meeting was arranged at what for me was an unusually early hour – at eight in the morning! And then the discussion was incredibly brief. After a quarter of an hour I was finished and I thought: "So was that all?" But I'd been accepted, and a few days later I had the acceptance in writing.

Epigenetics was still a new subject then. Did you have to convince Harald zur Hausen?

No, he is himself a virologist. He knew that epigenetic changes in viruses can silence genes, a process in which methylation plays a crucial role. My idea was to transfer this concept to cancer research. He found it interesting and obviously thought it must have some future.

And how has epigenetics developed in cancer research?

There's no stopping it! These days, we no longer look to see whether individual genes are methylated or not, we start with the entire genome. Epigenetics has developed into epigenomics. We know the enzymes that transfer the methyl groups, the methyltransferases. We know that epigenetic changes are not restricted to DNA and that proteins can also be affected. Here it's not only methylation, but acetylation that takes place, for example, and there are already drugs on the market that act on methylation.

Do you see the Nobel Laureate nowadays?

Of course we don't meet regularly any more. But a little while ago we were invited to the same dinner and he was very interested in my research. We talked for a long time. I always looked up to Harald zur Hausen, even before the Nobel Prize, because he was so tenacious in his pursuit of his idea that viruses can trigger cancer. From the discovery of the scientific basis to its clinical use in people. For me personally, that's the supreme

goal – to do research that is relevant to patients and to make sure our findings are used in clinical practice. And if the link between research and clinical practice is a lot closer now than it used to be, that's due in large measure to the initiative of Harald zur Hausen. And I'm really grateful to him for that.



Professor Frank Lyko heads the Epigenetics division. He has received many awards for his work. In 2004, the journal Technology Review selected him as one of the 100 most innovative young scientists in the world.



Harald zur Hausen receives the "Key to the DKFZ" from his predecessor Otto Westphal on May 1, 1983.

"A STROKE OF LUCK FOR THE DKFZ"

Transformation into a world-renowned research center

In the mid-1970s, the German Cancer Research Center did not have the best reputation, and some even felt the institution had lost its way. The low point probably came on March 6, 1976, when Rainer Flöhl, at the time Chief Science Editor of the Frankfurter Allgemeine Zeitung, described it as suffering from "both lack of leadership and inadequate competence in its field." The diagnosis could scarcely have been more damning.

Peter Krammer, who started working at the DKFZ as a young scientist in the crisis-ridden 1970s, vividly recalls the way things used to be: "It was a tricky situation back then. Things had really gone awry." The DKFZ was publicly criticized for pocketing

funds and publishing far too little, there was infighting among the directors, and even the scientists were at daggers drawn as they each jealously guarded their own turf. In Krammer's words: "We needed to get our act together – and fast."

Writing again about the German Cancer Research Center on its 40th anniversary in 2004, Flöhl gave the DKFZ scientists top marks. In his opinion, the Center had survived its teething troubles, and its scientists were now at the top of the publication and citation rankings. Some might even be considered for the Nobel Prize...

Nor was Flöhl, by then the dean of German science journalism, sparing in his praise for Harald zur Hausen, the man who had succeeded in putting an end to the internal strife and creating an atmosphere in which scientific creativity could thrive. "His perseverance, clear principles, and cogent concepts" had turned a "motley crew" into an institution engaged in top-flight research.

A remarkable turnaround. Looking back, says Krammer, it took zur Hausen a surprisingly short time to push through the long overdue reforms and give the DKFZ a new image. This success, or so Krammer believes, was due first and foremost to zur Hausen's personality as an integrator and to the purposeful way in which he gradually prepared the ground for a change of direction.

One of the biggest changes was the internal review system introduced soon after zur Hausen took office on May 1, 1983. Together with members of the Scientific Council, the Management Board carefully scrutinized the DKFZ's various divisions. The researchers were asked to report on their hypotheses and findings and to outline their objectives for the future. The internal presentations were then supplemented by regular external evaluations. As Harald zur Hausen himself explains: "We always attached the greatest importance to recruiting the best people in their field." These international evaluations were new back then, but these days are a standard management tool in almost every research institute. The evaluations have proven to be what the DKFZ hoped they would be: not authoritarian controls, but measures designed to promote quality, create transparency, generate interdisciplinary concepts, and distribute resources where they are needed. "Sometimes it was a little too much of a good thing," admits Peter Krammer; but in the end, everyone realized how they personally and the DKFZ as an institution could benefit from the reviews.

The scientists ultimately relinquished their initial skepticism and accepted the regular reviews. That they did so, Krammer feels, had a lot to do with the fact that zur Hausen remained a researcher among researchers, and hence one whose ability to assess their work in the lab they could trust. "He was of course an administrator," says Krammer, "but at the same time

represented the scientific community. And he is held in high esteem for that, even today." The traits that make a scientist – love of experimentation and fascination with the evolution of knowledge – are "a passion that has always driven Harald zur Hausen," opines Krammer.

The second fundamental change came about in the early

1990s. The eight independent institutes, each with its own director, were replaced by Research Programs, each represented by a spokesperson. This flexible structure was necessary to cope with the interdisciplinary demands of modern cancer research. Just how insular and rigid the institute's structure had been, and how high-handedly some institute directors





Top: German Research Minister Heinz Riesenhuber attends the inauguration of the first laboratory for Applied Tumor Virology, 1987.

Bottom: Visit from Lothar Späth, Premier of Baden-Württemberg, 1990.



German Research Minister Jürgen Rüttgers (second from right) acquainting himself with the DKFZ in 1995. From left: Head of Press and Public Relations Hilke Stamatiadis-Smidt, Professor Ethel-Michele de Viliers, Member of Parliament for Heidelberg Dr. Karl A. Lamers, and Professor Harald zur Hausen. could behave, was dramatically demonstrated immediately after zur Hausen took office, when one of the directors simply locked the doors of his institute!

With greater flexibility, quality assurance, and international connections all in place, zur Hausen began to treat a serious birth defect of the DKFZ - the absence of a link to clinical practice, which was a shortcoming that set the German Cancer Research Center apart from most of the world's major cancer research institutes. The original idea had been different. Paragraph 1 of the draft constitution for an "Institute for Tumor Research and Treatment in Heidelberg" of 1958 states that the task of the new institute shall be to "conduct research into cancer and treat cancer patients." Even Karl Heinrich Bauer, the inspiration behind the Center eventually opened in 1964, stressed time and again that it should be about people. No one wanted an "institute for the tumor pathology of rats and mice." There was cancer research on the one hand and clinical practice on the other, but only from the interplay of

the two could there be any real progress. He therefore advocated a close link between the new research institute and the University Hospital, proposing that the DKFZ have its own clinical units. Neither of these suggestions produced any results at first.

But that, too, changed for the better when Harald zur Hausen took office. Both clinicians and scientists engaged in basic research began to realize that since their efforts were meant to focus on cancer patients and their well-being, close cooperation was essential. In addition to the Heidelberg-Mannheim Tumor Center established in 1979, structures were created to foster cooperation in what was sometimes an uneasy alliance. In 1992, at the initiative of Harald zur Hausen, the University Hospital and German Cancer Research Center decided to set up clinical cooperation units, whose purpose would be to translate research findings into clinical practice as quickly as possible. There are now nine such 'clinical bridges.' Then, in 2004, the National Center for Tumor Diseases Heidelberg (NCT) was founded as a cooperative venture by the German Cancer Research Center, Heidelberg University Hospital, Thorax Clinic Heidelberg, and German Cancer Aid. The NCT's mission is to link patient care with state-of-the-art cancer research. The NCT, which will move into its new premises at the end of 2009, was also a brainchild of Harald zur Hausen and was initiated while he was still in office.

As a physician, zur Hausen also realized the importance to cancer patients of medical information from independent sources. Together with the then Head of the DKFZ's Press and Public Relations Department, Hilke Stamatiadis-Smidt, he created the Telephone Cancer Information Service to provide information for patients and their families.

"He's a doer," remarks Peter Krammer. And a man of many talents whose idiosyncrasies were not infrequently a cause of annoyance – as when he insisted on scheduling board meetings at eight o'clock in the morning. "Of course that served a purpose," says Krammer. "With everyone else still half asleep, he was invariably able to push through his ideas."

Harald zur Hausen combines many outstanding character traits, says Krammer, from a feel for excellent science and a great nose for talent to political and diplomatic skills and the conviction – in his day not exactly widespread in scientific circles – that people who are doing good

things should talk about them and so need a sympathetic press as well. All of which have made him "a stroke of luck for the DKFZ."





Top: Harald zur Hausen and Professor Rainer Haas, Head of the Clinical Cooperation Unit Molecular Hematology/Oncology, 1996.
Bottom left: When Harald zur Hausen retired in March 2003, one of the quests was the then Mayor of Heidelberg Beate Weber.

"OUR TASK IS TO BUILD ON THIS SUCCESS"

Interview with Dr. Josef Puchta, the Administrative-Commercial Director of the DKFZ

The senior managers' new offices at the German Cancer Research Center (DKFZ) reflect the organization's self-confidence, openness, and transparency. For visitors, the hushed corridors are like an oasis of peace in the middle of a construction site. Building means development and momentum, and that is what is happening at the DKFZ.

Dr. Puchta, the German Cancer Research Center is one big building site. It looks like everything is being turned upside down.

Dr. Josef Puchta: What you see here is total renovation in progress – but it's still business as usual. The main building is being fixed up in two stages – all eight stories of it. Next we intend to enlarge and modernize the animal building and to put up a radiology research and development center in the immediate vicinity. Unfortunately, this means a lot of noise and inconvenience for the people working here, but in the main

building at least, the worst will be over by the end of 2009. We want to make the building fit for the future. And for me that means constantly improving the quality of the facilities and fostering the scientists' creativity by providing suitable working conditions.

How many people work in the Center?

Our main building was originally designed for 800 people. In recent years, we've expanded a lot and right now have about 2,500 employees.



The futuristic building for the 7-Tesla highfield scanner symbolizes what the DKFZ as a whole aspires to provide: outstanding working conditions to attract the best minds.



The major renovation work currently in progress at the DKFZ should be completed in 2010.

You joined the DKFZ as Administrative-Commercial Director in 1996. What were your first impressions?

I saw the job as a great challenge, both because of the size of the institution and because of its focus. This is no place for figureheads. What made it easier for me was inheriting a team of very good people who were able to handle the day-to-day business without my help. They were people I could count on and together with them I was able to work on the Center's processes at a very high level. I think I can safely say that the Center's commercial operations and infrastructure are in great shape right now.

And how would you describe your first encounters with the Scientific Director Harald zur Hausen?

Well frankly, in the first few weeks it was rather like meeting an icon face to face. At least that's how a lot of people approached him. He also radiated a certain aloofness at first and I wasn't sure whether we'd be able to work together. But despite our very different mentalities, our mutual esteem grew quickly and the seven years we worked together were an interesting and enriching time. And I'm proud to say that since then we've become friends.

What character traits struck you in your dealings with Harald zur Hausen?

What impressed me most about him is how self-disciplined and organized he is. His time management is remarkable. Many things take him no more than a minute, and he frequently gets through a discussion in no more than a quarter of an hour, at most half an hour. There's the famous clock he always had in front of him, which at times inspired me to sit with a clock in front of me, too – not that it helped much! But there's no question that if it was really important, he always took the time required. What I also find very impressive is his ability to consciously and intensively think his way into people and situations.

When he was awarded the Nobel Prize, a great deal was written about his extraordinary perseverance. Did that strike you, too?

Yes, indeed. That's something that I would stress, too. And he's tenacious and persistent in all areas, not just those relating to his research. But the doggedness comes hand in hand with elegance, great self-assurance, fierce ambition, and a tendency to understatement. He's a highly interesting and very complex person. The world would be poorer if it didn't have such people.

Harald zur Hausen was very successful as a science manager. What was his secret?

I once told Harald zur Hausen that I know of nobody with such a natural gift for so much of what people are taught at management school. He always tackled problems intuitively, with a great talent for leadership and organization. And he was visionary in recognizing paradigm shifts, without ever being a slave to the latest trend. I think in case of doubt he'd rather swim against the tide than with it. That's a character trait we have in common. He showed great foresight in discerning the potential of new areas of research - genomics, for instance - and lost no time in recruiting the best people for the DKFZ; scientists like Peter Lichter, Annemarie Poustka, and Christof Niehrs. to name but a few. He's also a strong integrator.

Whether his management style has anything to do with current management practices is another question. In fact, the question doesn't even arise. In this business, the only thing that really counts is success, and he's certainly been successful. No doubt about it. In any case, there's no such thing as a management style that promises success, even in modern management. What's important is an authentic management style. And Harald zur Hausen is authentic.

What is the significance of the Nobel Prize for the DKFZ as an institution?

The prestige the prize bestows is so powerful that it reflects on the DKFZ, too. It's a fantastic thing for everybody working here, especially the young people and the PhD students. And it's also very emotional. The most moving moment for me – more emotional that the awards ceremony in Stockholm - was the improvised party on the afternoon of October 6, the day the prize was announced. At the invitation of the DKFZ Management Board, well over 1,000 people came over to the Communication Center to applaud Harald zur Hausen. And the applause was never-ending! It was phenomenal, truly aweinspiring, the kind of thing that happens only once in a lifetime. I saw many a veteran employee cheeks. It has also had a big impact outside the DKFZ, both here in Germany and abroad. The Nobel Prize is the seal of quality par excellence. It means you're playing in 'the big leagues.' The dimension the Nobel Prize has in people's minds is indeed astounding.

What comes after the Nobel Prize? Where does the German Cancer Research Center go from here?

Well as Germany's former national soccer coach Sepp Herberger used to say: "After the game is before the game." Our task is to build on this success, which certainly won't be easy. The DKFZ is rather like a large opera house – we also have our prima donnas. But that's also the beauty of it – being able to see these stars in action and admiring them for their success. We have excellent researchers. and our task is to continue attracting the best people. One of my most important jobs, therefore, is to ensure that the DKFZ has the financial resources it needs. Only then can we provide the infrastructure our scientists need to work creatively and successfully. One thing is already clear: In the next few years, we'll have to move into high gear financially. Only then can we safeguard the high scientific quality of the German Cancer Research Center and keep pace with the generously funded international research centers with which we have to compete. The nicest email that I personally received in connection with the Nobel Prize came from one of my colleagues at the Hebrew University in Jerusalem, who wrote: "Congratulations. Welcome to the club!" You can hardly put it more concisely than that.





The German Cancer Research Center (DKFZ) is one of the world's leading biomedical research institutes. Its mission is to systematically investigate the mechanisms of cancer pathogenesis and to detect and define the risk factors. The findings from this basic research are used to develop new approaches to prevention, diagnosis and treatment.

Employees	2165
Scientists	971
Guest scientists	164
Technical personnel	850
(As of Dec. 31, 2008)	

The German Federal Government provides 90 percent of the funding of the German Cancer Research Center, and the State of Baden-Württemberg the remaining 10 percent. Additional income stems from outside funding, license revenues, donations, and bequests.

The 42 scientific divisions, 15 junior research groups and 9 clinical cooperation units are assigned to seven Research Programs:

- Cell Biology and Tumor Biology
- Structural and Functional Genomics
- Cancer Risk Factors and Prevention
- Tumor Immunology
- Imaging and Radiooncology
- Infection and Cancer
- Translational Cancer Research

Account for donations

Deutsche Bank Heidelberg Sort code 672 700 03 Account no. 0157008

Imprint

Published by

German Cancer Research Center in the Helmholtz Association

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Edited by

German Cancer Research Center Press and Public Relations Im Neuenheimer Feld 280 D-69120 Heidelberg presse@dkfz.de www.dkfz.de

Design concept

Dagmar Anders, Different Arts, www.different-arts.de

Translation

Bronwen Saunders

Printed by

CITY-DRUCK HEIDELBERG

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