

10 Years Office of Technology Transfer

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October 2007

OFFICE OF TECHNOLOGY TRANSFER: A DECADE'S WORK PAYS OFF FOR THE GERMAN CANCER RESEARCH CENTER



Dr. Ruth Herzog, Head of the Office of Technology Transfer

The Office of Technology Transfer of the German Cancer Research Center (DKFZ) was founded in 1997 in response mainly to the German government's drive to promote patents. In the initial phase of the Office's work, the focus was on convincing scientists that there was just as much distinction in patenting as in publishing. Patents were "in" and within a short time the DKFZ had succeeded in significantly increasing the annual number of patent applications and in concluding the first license agreements. The focus on patenting, however, came at a price. To control the rising costs, therefore, the Office of Technology Transfer had to become more selective when deciding which patents to submit. As a result of this helpful learning phase, we are now able to focus on the professional and process-oriented exploitation of patents.

In line with its motto "**Your science is our business,**" the DKFZ at present has a dynamic patent portfolio of 224 inventions that is regularly updated and selectively marketed. License agreements are swiftly concluded and subsequently monitored. The financial revenues now being received from such agreements demonstrate that the work and effort put into technology transfer are worthwhile. One product in whose development the DKFZ is involved is playing an

especially important role here: the world's first vaccine against human papilloma viruses (HPV), a product of which the DKFZ is particularly proud.

Ten years after it was first founded, the Office of Technology Transfer already has a respectable track record. Between January 1997 and December 2006, we submitted patents for 347 inventions and concluded 182 license agreements and 154 cooperation contracts with industry. The patent costs of 12.9 million euros are offset by the 11.5 million euros in revenues from licenses and 12.6 million euros in cooperation proceeds. The German Cancer Research Center's spin-offs have also developed well, and new spin-off projects are being prepared. Alone the Siemens subsidiary that is a spin-off of MRC Systems GmbH now employs 70 people in Heidelberg. An additional 170 jobs have been created from DKFZ spin-offs, including the Steinbeis Technology Transfer Centers.

This success is primarily a result of the first-class basic research being done at the DKFZ as well as our open communication culture and continuous improvements in technology transfer processes. The foundation is a database we have developed ourselves which all technology managers can use to review the status of their patents and projects at any time and to manage all their contacts. To



The team of the Office of Technology Transfer (from left): Dr. Christine Amshoff, Dr. Volker Cleeves, Dr. Frieder Kern, Regina Otto, Sandra Schuhmacher, Gabriela Hantke, Dr. Ruth Herzog, Dr. Christian Kliem



Professor Wiestler: "What needs to be done is to close the gap between the laboratory and the patient's bedside. That's why new alliances are needed, bringing together hospitals, research and industry."

become even more efficient, in 2002 we invited international experts to evaluate our work and one year later had ourselves benchmarked against cancer research institutes in the United States. We received gratifyingly good marks, but were also able to identify areas requiring improvement, for which we designed and implemented a series of measures. The "spring cleaning" was thorough: We systematized our process for selecting inventions, examined patents for their economic potential and sustainability and revitalized our marketing. We also streamlined our contractual operations in order to reduce the time to closing a deal.

By marketing the results of its research, the DKFZ hopes to strengthen innovation in Germany. The expectations are high: Which new cancer drugs will help patients? Which are the next blockbusters? How do we exploit the creative potential at the DKFZ for the well-being of cancer patients? How do we create organizational structures for translational research, i.e. putting scientific findings into clinical practice? The Chairman of the Board and Scientific Director of the DKFZ, Professor Otmar D. Wiestler, a committed pioneer of translational cancer research in Germany, explains: "What needs to be done is to simplify and speed up the translation of the latest findings in research into clinical practice and so close the gap between the laboratory and the patient's bedside." Methods that were once the

purview of industry, such as the production of cancer drugs under controlled, standardized conditions to GMP (Good Manufacturing Practice) or the identification of techniques, target molecules and substances, chemical modification, in vitro and in vivo testing, are finding their way into research at the DKFZ. These efforts are being backed up by new organizational forms such as the National Center for Tumor Diseases (NCT), established along the lines of the Comprehensive Cancer Centers in the United States. In addition, the DKFZ has created an intramural support program to selectively promote translational research projects. The DKFZ also maintains a chemical biology core facility together with the European Molecular Biology Laboratory. "But this is just the beginning," says Otmar D. Wiestler:

WORKFLOW TECHNOLOGY TRANSFER

| Find | Market | License | Manage |
|---|--|--|---|
| <ul style="list-style-type: none"> Find, evaluate, select inventions Build relationships with inventors Identify collaboration opportunities Secure intellectual property rights | <ul style="list-style-type: none"> Prepare technology abstracts Search for licensees and collaboration partners Exchange information with potential industrial partners (under CDA) Sell the technology | <ul style="list-style-type: none"> Negotiate terms of agreement Draft and revise contract Close the deal | <ul style="list-style-type: none"> Collect royalties Build relationships with licensees Controlling of agreements |



“Cancer research will be more targeted, more individualized and more interdisciplinary in the future. That’s why new alliances are needed, bringing together cancer research, clinical oncology, the pharmaceutical industry and medical technology firms. We’ve succeeded in creating a strategic alliance of this kind with Siemens in the field of radiology. Now we’re seeking something similar with a pharmaceutical partner.”

Nowadays in the pharmaceutical industry, one in two new drugs is licensed in.

The buzzword is “open innovation.” In a world of global competition, even the most powerful industry leaders need partners to survive. Yet most cooperation takes place close to the market and less in the area of basic research. The DKFZ is therefore moving to close the gap with industry through application-driven activities such as technology transfer, the NCT Heidelberg and the chemical biology core facility. This could give rise to new – and mutually beneficial – models for efficient cooperation between industry and the DKFZ.

With programs such as GO-Bio and the High-Tech Strategy, government research and technology policy is creating favorable conditions for technology transfer. The key question to be asked when considering cooperation with industrial companies is: “To whom do the inventions belong?” The DKFZ grants companies rights of use against payment for any discoveries made in the course of a cooperative agreement because we want to benefit in the event of success. In the past, we have almost always gained acceptance for this demand. Fortunately, the German government is sensitive to this crucial issue and has prepared a brochure on the subject of cooperation between science and industry, providing concrete assistance with drawing up contractual agreements. After all, the success of technology transfer benefits everyone – in particular cancer patients, whose treatment

CLINICAL PIPELINE

| | Research and Development | Preclinical | Phase I | Phase II | Phase III |
|--------------------------------|--|-------------|---------|----------|-----------|
| Palladium complex | ● | | | | |
| Betulinic acid derivatives | ● | | | | |
| DMNT1 inhibitor ⁽¹⁾ | ● | | | | |
| HC Toxin ⁽²⁾ | ● | | | | |
| Griseofulvin analogue | ● | | | | |
| Riproximin | ● | | | | |
| H1 virus | ● | | | | |
| Anti-L1-Antibody | | ● | | | |
| MGMT-Inhibitor ⁽³⁾ | | ● | | | |
| Thioplantium | | ● | | | |
| CD95Fc | | ● | | | |
| Methotrexate-HSA | | | | ● | |
| Glufosfamide | | | | | ● |
| HPV Vaccine ⁽⁴⁾ | Gardasil® approved in > 70 countries, Cervarix® approved in Australia and Europe | | | | |

(1) DNA (cytosine-5-)-methyltransferase 1
 (2) Helminthosporium carbonum

(3) O6-Methylguanin-DNA methyltransferase
 (4) Human Papilloma Virus



Technology transfer alliance of the DKFZ, EMBLEM, Heidelberg University Hospital and Medical Faculty (from left): Dr. Volker Cleeves (technology manager for the University Hospital), Dr. Martin Raditsch (EMBLEM), Dr. Jörg Rauch (technology manager for the University Hospital), Dr. Ruth Herzog (DKFZ)

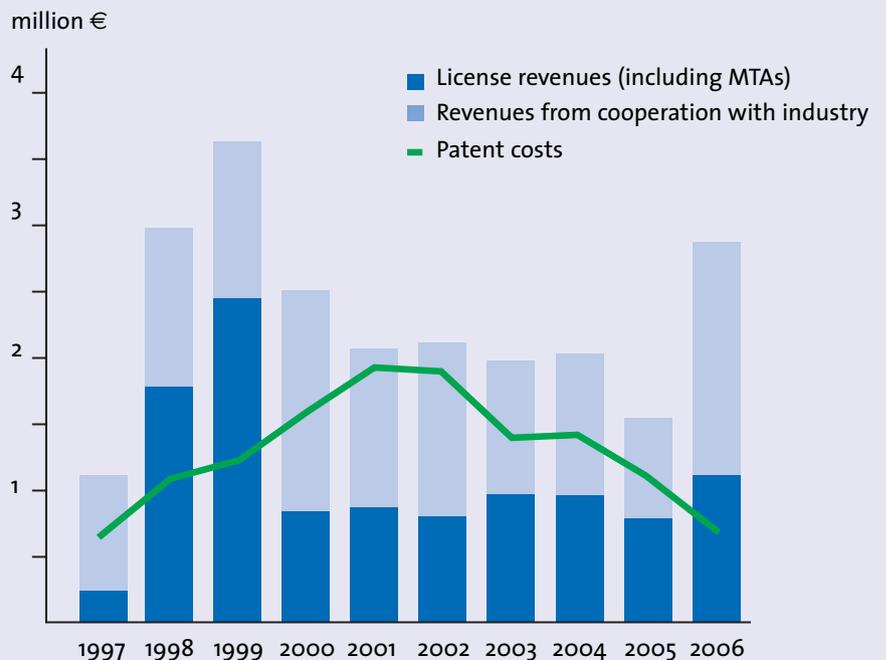
can be improved by new methods and active substances, but also companies, for whom having access to innovations means remaining competitive, the DKFZ, which can reinvest the revenues from licenses in research, and – of course – the scientists, whose research bears fruit.

In order to continue building up the efficiency and sustainability of technology transfer at the DKFZ in the years ahead, we are extending our alliance in Heidelberg with EMBLEM, the technology transfer company of the European Molecular Biology Laboratory. Since January 2007, the DKFZ and EMBLEM have together been organizing technology transfer for the Heidelberg University Hospital and Faculty of Medicine. The University Hospital and Medical Faculty are therefore using the expertise of the two technology transfer partners, with their years of experience, to get off to a fast start. The aim is to generate revenues as quickly as possible that can be reinvested in research. Here, the DKFZ Office of Technology Transfer can leverage the database it developed in-house, which permits the electronic linkage of documents from different projects and the use of the data at all three locations – the University Hospital, EMBLEM and the DKFZ. Two new co-workers, Dr. Volker Cleeves and Dr. Jörg Rauch, have been working as scouts and technology managers on the University campus since August 1, 2007.

HPV VACCINE: A SUCCESS STORY

The world's first vaccine for human papilloma viruses (HPV) has been on the market since June 2006. The vaccine, produced by the US manufacturer Merck & Co. under the trade name Gardasil®, provides prophylactic protection against HPV 16 and 18, which account for about 70 percent of all cases of cervical cancer, and against HPV 6 and 11, which cause around 90 percent of all genital warts. Two scientists from the German Cancer Research Center, Professor Harald zur

REVENUES AND COSTS 1997 – 2006





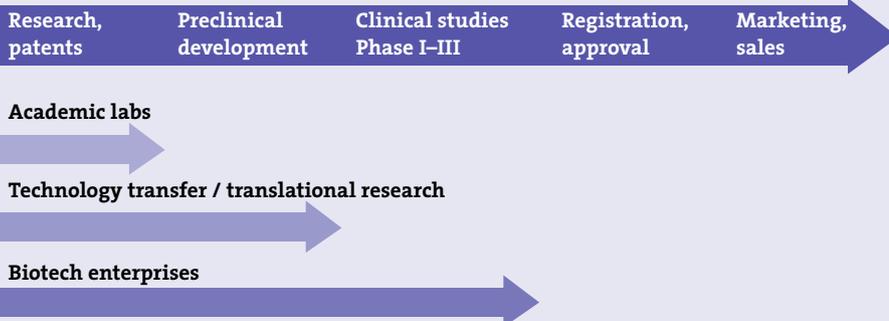
Hausen, a virologist and for many years Scientific Director of the DKFZ, and Professor Lutz Gissmann, Head of the Division of Genome Modifications and Carcinogenesis, played a key role in the development of the new vaccine.

Gardasil® has gotten off to a spectacular start. Sales in the past year totaled 235 million US dollars. In the first quarter of 2007, Merck & Co. generated revenues of 365 million US dollars in the United States alone. The product has now been registered in more than 70 countries. One decisive factor in the success of Gardasil® was the rapid decision-making by the vaccination authorities, in particular the CDC Advisory Committees on Immunization Practices in the United States. A number of US states subsequently initiated vaccination programs for girls aged nine to twelve. According to a conservative estimate by Goldman

Sachs, sales of Gardasil® will total around 2.5 billion US dollars in 2010, while Lehman Brothers and Morgan Stanley are even forecasting revenues of over four billion dollars. All these estimates include uses that go beyond the recommendations of the vaccination committee or the registered indications. In the early years, the “catch-up” population of girls and women aged 13 to 26 will probably generate high sales revenues.

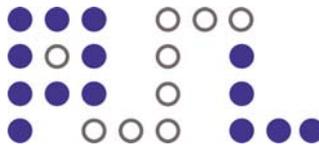
Cervarix®, the HPV vaccine made by competitor GlaxoSmithKline and developed parallel to Gardasil®, has been available in Australia since May 2007 and has just been approved (in September 2007) in Europe, too. Its registration in the USA is likely to follow in the first quarter of 2008. GSK is currently comparing the two vaccines in a clinical trial, and the initial results are expected in the second half of 2007. Given the head start of Gardasil®, experts believe that Cervarix® will not be able to capture a market share of more than 40 percent.

THE CHALLENGE OF CLOSING THE GAP ...



LICENSES

The license agreement concluded with the U.S. firm **Accuray** Inc. in March 2007 is a classic example of how a cooperation commitment can evolve into a license contract. Accuray is an American company that has developed a product it calls the “Cyberknife® System.” With the



help of this unique, robot-assisted radio-surgical precision technique, it is possible to treat tumors anywhere in the body with an accuracy in the sub-millimeter range. Supported by imaging techniques, the Cyberknife® System can track the movements of the patient – and thus of the tumor – during treatment; this makes invasive methods to keep the patient's position fixed unnecessary. The core of this technology is an iris diaphragm, which acts as a collimator to bundle the rays. This invention by Dr. Gernot Echner of the Division of Medical Physics at the DKFZ headed by Professor Wolfgang Schlegel, is a further development in the field of stereotactic radiation therapy of tumors.

Since February 2007, the French company **Waypharm** SAS has been the new licensee of the thioplatinum technology of Dr. Eberhard Amtmann of the Division of Tumor Progression and Tumor Defense at the DKFZ. As part of an option agreement, Waypharm is attempting to manufacture a stable liposomal formulation of the substance TP2 on an industrial scale; if it is successful, it will initiate phase I clinical trials. In the low-oxygen conditions in solid tumors, thioplatinum derivatives exhibit both heightened activity and selectivity for tumor cells.

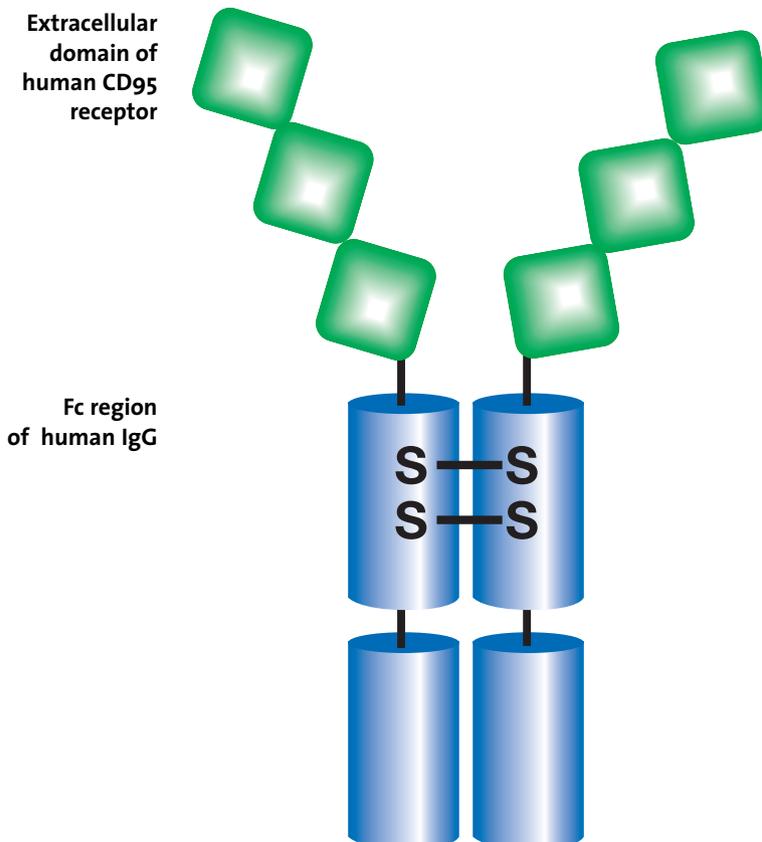
The Norwegian firm **Affitech** AS is developing therapeutic antibodies from its own antibody libraries, produced in part with the aid of a patented DKFZ

invention based on phages. This phagemid, known as a “Breitling patent,” is one of the basic patents in the field of phage-based antibody development. The DKFZ is therefore participating in the milestones and revenues of Affitech AS from the development and licensing of therapeutic antibodies. On the strength of various license agreements, Affitech AS has substantially improved its patent position in recent months, for instance through cross-licensing with Dyax and Xoma, two American firms, and through a license and cooperation contract with F. Hoffmann-La Roche AG, Basel, in May 2007. Affitech, moreover, possesses in-house technologies such as AffiSelect™, AffiScreen™, and the CBAS™ technology that enable it to identify specific binding structures of living cells with the aid of antibody libraries.

The license and cooperation agreement of the DKFZ with **ProSkelia** SAS, Paris, exemplifies the changes that a long-standing collaboration can undergo over the years. The agreement originally covered licenses to discoveries made by Professor Christof Niehrs, Head of the Division of Molecular Embryology, including the so-called Dickkopf protein Dkk-1, an important control protein in bone development. As a result of various transactions within the company, the agreement has had to be updated on a number of occasions, as in 2004, when ProSkelia merged with the Scottish firm Strakan, giving rise to ProStrakan. In



TARGET STRUCTURE OF THE FUSION PROTEIN APG101



December 2006, the Belgian firm Galapagos acquired ProSkelia and has taken over the agreement concluded with the DKFZ. The collaboration developed so successfully that it was further expanded. In July 2007, the DKFZ signed a license contract with Galapagos, this time covering a new invention by Niehrs and his team.

COOPERATION AGREEMENTS

In 2006, the German Cancer Research Center received 1.85 million euros from cooperation agreements with industry. The strategic alliance between Siemens and the DKFZ has been developing satisfactorily since their agreement was signed in January 2006. As a result, Siemens and the DKFZ recently signed supplementary agreements on magnetic resonance tomography and the evaluation of new algorithms for tumor diagnosis (the Radiology Division headed by Professor Ulrich Kauczor) and on the 7-Tesla ultra-high field nuclear magnetic resonance tomograph (Division of Medical Physics in Radiology headed by Professor Wolfhard Semmler). As part of this strategic alliance, the DKFZ has licensed out more than 20 inventions (patents and software) to Siemens, including the inventions originally licensed out to MRC Systems GmbH and the discoveries made jointly by the DKFZ and the Gesellschaft für Schwerionenforschung mbH (GSI), Darmstadt, in the field of particle therapy.



SPIN-OFFS

After a lengthy dry spell, the number of planned spin-offs at the German Cancer Research Center is increasing again, partly with the support of the Helmholtz Association. The DKFZ spin-offs that are already in operation will soon have their first products in clinical trials. However, various milestones still have to be reached before the products can be launched – at the earliest in 2010. Providing the product candidates and companies continue to develop successfully, the DKFZ will benefit both from the equity it holds and from royalty payments from the spin-offs.

Affimed Therapeutics AG concluded a major round of financing in April 2007, the 25 million euros it raised being enough to give the company financial security until 2010. The consortium of international venture capital investors includes BioMedInvest, OrbiMed Advisors and Life Sciences Partners, plus the seed capital investor FirstVentury. The financing should enable Affimed to continue developing antibody projects in a highly competitive market for clinical phases. Should the two preclinical antibody projects be successful in Phase IIa, the consortium would be available for further funding. Affimed Therapeutics AG also settled two patent disputes in its favor this past year.

Apogenix GmbH, which was relaunched at the end of 2005 with a new management team and a fresh injection of capital (15 million euros), is performing well.

One piece of good news for Apogenix was that the European Medicines Agency EMEA has recommended granting orphan drug status to APG101, a fusion protein which can prevent graft-versus-host disease (GvHD). Apogenix hopes to begin the clinical development of APG101 for this indication in the first quarter of 2008. APG101 inhibits programmed cell death (apoptosis), which is instrumental in causing organ damage in GvHD, by blocking the interaction between the CD95 ligand and the CD95 receptor. GvHD is triggered when immune cells of the bone marrow donor (“graft”) destroy the tissue of the recipient (“host”). The disease, which often ends fatally, occurs mainly in leukemia patients in whom allogenic bone marrow (i.e. taken from a donor) is transplanted after their own bone marrow has been destroyed by disease. Approximately 8,000 allogenic bone marrow transplants are performed annually in the European Union (EU).

The EMEA can grant orphan drug status to substances for the treatment of severe or life-threatening illnesses if no more than five in 10,000 people in the member states of the EU, Norway, Iceland and Liechtenstein are affected by the condition. This status gives the company exclusive marketing rights for a period of one to ten years after marketing approval.



Dr. Michael Boutros: "The Office of Technology Transfer provides us with ongoing assistance and support in the development and implementation of the GO-Bio concept."

mtm laboratories AG is developing test systems for the in vitro diagnosis and early identification of cervical cancer. Its products include the CINtec® Histology Kit and the CINtec® Cytology Kit, which the company has been marketing internationally since January 2007. The kits, which are available in Europe and the US as CE-marked medicinal products, are based on the patent-protected biomarker p16INK4. In order to prove its clinical benefits, the clinical research team has been enlarged this past year and mtm laboratories AG has hired new staff for marketing and distribution.

Helmholtz Enterprise is the program of the Helmholtz Association for the pro-

motion of spin-off projects. The DKFZ participated in seven applications in 2006/2007, five of which have received support. The spin-off founders receive 200,000 euros for one year as a rule, half of which is provided by the Helmholtz Head Office and the other half by the DKFZ.

The winner of the first funding round under the GO-Bio scheme of the Federal Ministry of Education and Research from the DKFZ is Dr. Michael Boutros, Head of the Boveri Group Signaling and Functional Genomics. He is aiming to identify new target structures for cancer drugs with the aid of RNA interference (RNAi), a technology that enables individual genes to be selectively silenced. Using an innovative high-throughput screening technique, that he and his team have developed tens of thousands of genes and their functions can be efficiently analyzed. Michael Boutros focuses on signal paths as points of attack since these are involved at a relatively early stage in the development of cancer. The method is to be applied to human cells and connected with the screening of substance libraries. The aim is to found a company that will work on the further development of the most interesting substance candidates up to the preclinical stage.

HIGHLIGHTS

- | **Excellent infrastructure**
 - ▶ **Own database since 1997**
- | **Peer assessment 2002**
 - ▶ **Positive, with specific recommendations**
- | **Benchmarking 2003**
 - ▶ **DKFZ compares well with US cancer centers**
- | **Strategic alliance with Siemens commenced in 2006**
- | **Significant revenues from the HPV vaccine**

DKFZ KEY FIGURES 2006

DKFZ Key figures

| | 1997 | 1998 | 1999 | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 |
|--|-----------|-------|------|-------|-------|-------|-------|-------|-------|-------|
| External research funding projects | | | | | | | | | | |
| Revenues from R&D projects with industry, in million € | 0.93 | 1.26 | 1.24 | 1.75 | 1.25 | 1.38 | 1.05 | 1.12 | 0.76 | 1.41 |
| External funding revenues, overall, in million €* | 17.53 | 24.23 | 27.3 | 27.60 | 30.40 | 29.23 | 33.28 | 31.12 | 31.50 | 36.90 |
| Collaborations with industry, number of | about 50 | 50 | 59 | 51 | 50 | 60 | 55 | 48 | 56 | 49 |
| Industry-related results | | | | | | | | | | |
| Patent families, number of | about 120 | 151 | 204 | 259 | 301 | 265 | 250 | 233 | 212 | 224 |
| Patent disclosures, number of | 41 | 75 | 71 | 62 | 61 | 42 | 29 | 36 | 36 | 45 |
| First patent filings, number of | 31 | 53 | 55 | 55 | 45 | 22 | 22 | 19 | 19 | 26 |
| Patents granted, number of | 49 | 67 | 39 | 26 | 104 | 82 | 137 | 48 | 60 | 60 |
| Patent costs, in million € | 0.61 | 1.06 | 1.18 | 1.63 | 1.94 | 1.90 | 1.35 | 1.38 | 1.12 | 0.70 |
| License agreements, number of | 26 | 19 | 56 | 83 | 84 | 82 | 105 | 105 | 94 | 89 |
| License revenues, in million € | 0.23 | 1.90 | 2.88 | 1.08 | 0.89 | 0.85 | 1.03 | 1.02 | 0.85 | 1.17 |
| Enterprise launches, number of** | 2 | 0 | 3 | 5 | 5 | 1 | 1 | 1 | 0 | 0 |
| Jobs from enterprise launches, number of | n.k.*** | 99 | 112 | 132 | 167 | 183 | 150 | 125 | 150 | 170 |

* excluding transitory funds

** including Steinbeis Transfer Centers

*** not known

Financial data

| | million € |
|----------------------------|-----------|
| Operating costs | 122.3 |
| Personnel expenses thereof | 76.1 |
| Institutional funding | 107.6 |

Staff

| | |
|------------------------------|----------------|
| Person-years, overall | 1,741.5 |
| Of these: Staff scientists | 492.2 |
| Doctoral students | 282.5 |
| Visiting scientists | 28.2 |
| Scientists altogether | 802.9 |

Source: DKFZ's progress report 2006



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