Dear colleague and business partner,

We proudly announce the launch of our newsletter which we have named CaRe2B – cancer research to business – to reflect both its origin, the German Cancer Research Center (DKFZ), and its aim to be a concise vehicle containing

• our novel patented technologies ready for out-licensing
• features on inventors and inventions and
• what is “hot” at the DKFZ and its technology transfer.

We kindly invite you to step into our first issue to learn more about the business side of the DKFZ. In this issue you will be introduced to the phase I clinical trial of glioblastoma with our H1 parvovirus technology. Featured in this issue are Holger Sültmann on genomics to diagnose prostate cancer and Jörg Hoheisel on pancreatic cancer.

CaRe2B will appear about four times a year in addition to our e-mail marketing of our technologies. We would appreciate your feedback!

Enjoy!

Cheers,

Ruth Herzog

Content:

Feature Articles on new diagnostic approaches to prostate cancer and pancreatic cancer
New Technologies: Diagnostics, Research Tools, Therapeutics, Vaccines, Devices
Patents granted
New and Notable: The phase I clinical trial of glioblastoma with DKFZ H1 parvovirus technology.
Spin-offs, Awards, Inside the office

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Prostate cancer is the most frequent tumor type in males, causing 6% of cancer deaths in men. The routine diagnostic procedure for prostate cancer is a prostate biopsy after the detection of elevated levels of prostate-specific antigen (PSA) in the blood, followed by an ultrasound investigation. However, due to the heterogeneous nature of the prostate tissue, tumor cells are frequently not found in the biopsies despite elevated PSA levels. In many cases, this leads to uncertainty as to the presence of malignancy and to patients having to undergo further biopsies and blood tests.

That's why Dr. Holger Sültmann and his team developed a new strategy for improving prostate cancer diagnostic procedures using histologically normal prostate biopsies. The team started from the hypothesis that morphologically detectable, malignant transformation of prostate epithelial tissues is preceded by considerable molecular changes. By analyzing gene expression changes in normal prostate biopsies, five genes were identified that displayed significantly different expression levels between three prostate cancer risk groups. These results were independent of age, PSA level, frequency and timing of previous prostate biopsies, tissue composition, tumor stage, and tumor grade. The transcript levels of these genes were found to be highly indicative of the presence or absence of cancer in the entire prostate. [Technology offer]

A second study using blood was undertaken to identify molecular changes that indicated the presence as well as the aggressiveness of prostate cancer. Dr. Holger Sültmann and his team screened serum samples of patients with metastatic (n=7) and localized prostate cancer (n=14). They identified five up-regulated miRNAs and, after a further validation study (n=45), miRNA-375 and miRNA-141 turned out to be the markers most indicative of aggressive (high risk) tumors. Their blood levels were correlated with a high Gleason score or lymph-node positive status in a second independent validation study (n=72). In addition, the tissue expression of the two miRNAs (36 tumor vs. 36 benign) was correlated with the findings in serum samples. [Technology offer]

These two new strategies, serum miRNAs and gene signature of prostate biopsies, have the potential to markedly improve future prostate cancer diagnosis – with minimally invasive diagnostic procedures – for the benefit of (suspected) prostate cancer patients.

Inventor profile

Dr. Holger Sültmann is head of the “Cancer Genome Research” working group in the Division of Molecular Genetics at the DKFZ. He and his group are based at the National Center for Tumor Diseases (NCT Heidelberg), enabling close contact between scientists and patients. It is the expressed aim of Dr. Holger Sültmann to translate his research results into clinical applications. In addition to diagnostics projects, he successfully initiated and established a German network on prostate cancer genome sequencing, which is part of the International Cancer Genome Consortium (ICGC) and which focuses on therapy and the causes of prostate cancer.
Pancreatic cancer is often called a “silent disease” because it typically does not cause symptoms early on. Thus, the cancer progresses for 15 years, on average, prior to diagnosis. At this late stage, the tumour is usually highly metastatic and non-operable. As a result, mortality is nearly identical to incidence. Early resection, however, increases the 5-year survival rate dramatically. Accordingly, early stage screening techniques are badly needed. These techniques should also be simple and robust so as to be applicable in a routine manner to people over 50 years of age.

DKFZ scientists Dr. Jörg Hoheisel and Dr. Christoph Schröder, in collaboration with Dr. Tatjana Crnogorac-Jurcevic (Queen Mary University of London), recently discovered a set of 27 proteins with high potential for non-invasive diagnosis. They exhibit highly significant abundance differences in urine samples of pancreatic cancer patients on an antibody array that targets 741 different cancer-related proteins. The data of the pilot study are currently being validated on several hundred samples from two patient cohorts of different clinics. Furthermore, a validation with several hundred samples provided by a European consortium is planned for the next two years in order to optimize both the individual marker proteins and the overall diagnostic signatures. Simultaneously, Dr. Hoheisel and his team are converting the current assay format into a routine immunodiagnostic kit.

Like the discovery itself, future findings will fundamentally improve detection, staging and grading of pancreatic cancer and will help in assessing treatment decisions. [Technology offer]

The inventors presented their new technology recently at the BioVaria (Munich) and the HUPO congress (Geneva).

Inventor profiles

Dr. Jörg Hoheisel is Head of the Division of Functional Genome Analysis and active in establishing and applying analysis techniques at the levels of DNA, RNA and proteins for the examination of molecular cellular functions. On this basis, biomedical systems are being developed for early and personalized diagnosis and prognosis of cancer, identification of new therapy approaches and monitoring of treatment success, with a focus on pancreatic cancer. During his PhD and postdoctoral work at the DKFZ, Christoph Schröder established protocols for the robust analysis of disease-relevant variations in protein expression and structure. Based on complex antibody microarrays, processes were established for proteomic studies that meet or exceed the requirements for an application in a clinical setting.
Protein Biomarkers for Non-invasive Diagnosis of Pancreatic Cancer (P-909)

A set of 27 proteins was identified at significant differential levels in urine of patients with pancreatic adenocarcinoma. This complete set of proteins or parts thereof can be used to support diagnosis, prognosis as well as treatment decisions. [Feature Article]

Antibody against Neurofibromin: Diagnostic and Prognostic Marker for Glioma Treatment (P-897)

The informative value of the DKFZ monoclonal antibody against neurofibromin 1 was proofed by using biopsy material. The antibody allows the fast and reliable detection of tumor cells by immunohistochemistry (IHC) and Western Blot analysis and is fast, reliable and ready to use.

Enhanced Diagnosis of Prostate Cancer with Serum miRNAs as Non-invasive Markers (P-892)

Since only 20% of prostate cancer patients need therapy owing to the fast progression of the cancer, DKFZ inventors developed a method to detect specifically those cases of aggressive and high-risk tumors. The two miRNAs identified can be detected relatively non-invasively in the serum of patients. [Feature Article]

Improving Prostate Cancer Diagnostic with Specific Gene Expression Signatures in Prostate Tissue (P-710)

DKFZ inventors identified five genes displaying significant differential expression between prostate cancer patients, healthy donors, and cancer suspected patients with continuous negative biopsies. [Feature Article]

Evi/Gpr177 as New Target for Treating and Diagnosing Brain Tumors (P-975)

DKFZ inventors identified the Wnt secretion protein Evi/Gpr177 as a new target, which is strikingly upregulated during glioma tumorigenesis in a stage-independent way and which correlates with poor prognosis. Silencing of the Evi/Gpr177 protein significantly inhibits glioma cell proliferation and migration.

Improved Yeast Two-Hybrid Screening by Next Generation Sequencing (P-920)

The current technology combines yeast two-hybrid screening methods with
massive parallel sequencing. This results in a cost reduction of more than 10 times and dramatically improves throughput of yeast two-hybrid screening. Thus proteome-wide interaction mapping in a single large yeast two-hybrid screen is possible.

**Synthetic Promoters for Research, Gene Therapy & Plant Biotechnology (P-903)**

DKFZ scientists have successfully applied a novel method for the rational construction of synthetic promoters which respond only to predefined transcription factors. The synthetic promoters developed have a broad application area as e.g. laboratory kit, in drug development, tissue engineering, virotherapy or plant biotechnology.

**New Perspectives with the Use of $[^{18}\text{O}_3]$-ATP and -GTP in Mass Spectrometry (P-872)**

To circumvent radioactivity labelling in phosphoproteomics, DKFZ inventors established a fast and cost-effective procedure to produce mass-labeled $[^{18}\text{O}_3]$-ATP and -GTP. Investigation of ATP or GTP-dependent reactions with mass spectrometry as the most powerful tool in proteomics thus became feasible.

**Fast and Reliable Detection of Contaminations in Cell Cultures (P-792)**

The present high-throughput technology based on multiplex PCR and Luminex detection provides means and methods to simultaneously detect up to 35 viral, microbial and inter-species contaminations. Additionally, it facilitates sensitive and cost-effective determination of cell line purity.

**Redesigned Bacterial Killers for the Treatment of Breast Cancer and Melanoma (P-834)**

DKFZ inventors redesigned E. coli to detect and kill cancer cells. The team headed by Prof. Dr. Roland Eils received several awards in different categories of the iGEM (international Genetically Engineered Machines) competition organized by MIT in Boston.

**HMGB1 for the Treatment of Tumors (P-798)**

The High Mobility Group B1 (HMGB1) protein belongs to the HMG family of nuclear proteins, which have been implicated in the pathogenesis of various disorders. DKFZ inventors now showed that HMGB1 efficiently kills human malignant glioblastoma tumor cells.
**VACCINES**

**Human Papillomavirus (HPV)-Vaccine Produced in Bacterial Cells (P-884)**

The current technology provides a vaccine with the capability to function both as a prophylactic and a therapeutic vaccine. Moreover, it can be produced in bacterial cells, which makes production very cost-effective.

**Synthetic Multifunctional Proteins Useful for Vaccination against Tumor Antigens (P-498 / P-836)**

DKFZ inventors demonstrated that virus-like particles consisting of multifunctional fusion proteins of one or more tumor antigen domain(s) and an immune stimulatory domain are highly immunogenic and induce strong cellular immune responses against tumor cells.

**Scaffold-stabilized L2 Peptides as HPV Vaccine (P-824)**

DKFZ inventors developed a thioredoxin-L2 vaccine, which can be produced in standard E. coli bacteria, allowing cost-effective production. Moreover, immunization against peptides from the L2 protein gives a robust immune reaction that provides cross-protection against a variety of other high-risk HPV strains.

**DEVICES**

**Multichannel Micro Strip Coil for In-coupling Travelling Waves in MR Imaging (P-972)**

The DKFZ-designed multichannel micro strip coils, using travelling waves, are based on a tripline concept. This reduces the electromagnetic interference, the risk of hotspot appearance at Highfield-MRI and minimizes the global specific absorption rate (SAR).

**Magnetic Position Sensor for Multileaf Collimators (MLC) (P-959)**

The invention describes a method using a Hall Effect sensor measuring the magnetic field of thin magnetic strips attached to the individual leaves of an MLC. The technology is robust to perturbations or disturbances and ensures an exact beam shape for radiation therapy.

**4D Imaging for Radiologically Guided Interventions (P-953)**

Image-guided interventions by continuous monitoring with MRI, but also CT, leads to a high radiation dose for the physician and the patient. We developed a radiologically guided intervention method, which monitors 4D imaging and lowers the radiation dose with only single shots during the intervention.

**Mobile On-patient Visualization Device of Medical Images (P-952)**

We developed a new concept for on-patient visualization of anatomical data
acquired with an arbitrary modality (typically CT or MRI). The method is based on a mobile device consisting of a flat display and a Time-of-Flight (ToF) camera which can be moved along the patient to provide a view of internal anatomical structures via augmented reality.

Coaxial Magnetic Resonance Tomograph (P-911)

DKFZ inventors developed a new coaxial design of a magnetic resonance tomograph, which is regarding position and size. The new coaxial design reduces the radio frequency exposure to the area investigated and therefore lowers the global specific absorption rate.

A list of all available technologies can be found here [Link].

Methods for Producing Antibody Libraries, Selecting and Humanizing Antibodies (P-488)

This patent was granted in the following European countries AT, CH, DE, ES, FR, GB, IT, NL, PT. The method of the invention is based on the technology in which a large and highly uniform number of antibodies are covalently attached to the surface of a eukaryotic cell, enabling comparable signals from cell to cell. Using this technology, specific antibodies can be selected out of a large number of cells together with the presenting cell.

Means and Methods for Diagnosing and Treating Cancer Based on the FRMD3 Gene (P-707)

This patent was granted in the following European countries CH, DE, FR, GB. DKFZ researchers found that FRMD3, a member of the protein 4.1O super family, is expressed in normal human lung tissue. In 54 out of 58 different primary non-small-cell lung cancer tumors, the expression of FRMD3 was silenced compared to patient-matched healthy lung tissue.

Using Viruses to Fight Brain Tumors – Bridging the Gap Between Research and Clinical Application

Parvoviruses can enter and kill cancer cells, but they do not cause disease in humans. Since 1992, scientists at the DKFZ have been studying these viruses with the aim of developing a viral therapy against dangerous brain tumors that are almost impossible to treat. The first ever phase I/IIa clinical trial has now started at the Neurosurgery Department of Heidelberg University Hospital to test the safety of parvovirus therapy. Developing this innovative treatment method to the stage of clinical application has been made possible through collaboration with Oryx GmbH & Co KG.
Roche Acquires DKFZ Spin-off mtm laboratories AG

MtM laboratories founded in 1999 was one of the first spin-offs from the German Cancer Research Center. The Roche Diagnostics division has now acquired it for 190 million euros. MtM laboratories is a leader in developing in vitro diagnostics with a focus on early detection and diagnosis of cervical cancer. (www.roche.com)

Mint Medical Releases mint Lesion™ 1.6 – a Major Step to Facilitate an Efficient Assessment of Tumor Therapies

The DKFZ spin-off Mint Medical aims at providing image processing methods to improve medical diagnosis, therapy planning, and computer assisted therapy. Like all its products, the new mint Lesion™ 1.6 software conforms to the European Medical Devices Act and bears the CE mark. (www.mint-medical.de)

Apogenix Successfully Completes Patient Recruitment for Glioblastoma Phase II Trial with APG101

Apogenix, founded in 2005, develops novel protein therapeutics for the treatment of cancer and inflammatory diseases. The company’s lead product candidate, APG101, is a fully human, soluble fusion protein combining parts of the CD95 receptor and IgG. APG101 successfully completed a phase I study in 2009. (www.apogenix.com)

From Microscopy to Nanoscopy: 2011 Meyenburg Award Goes to Stefan Hell

The EUR 50,000 Meyenburg Award in 2011 goes to physicist Stefan Hell for his role in developing a whole new kind of light microscopy. His discovery makes it possible for the first time to observe living cells down to nanomolecular scale.

Prestigious Research Award for Young Cancer Researcher

Christian Stock, a scientist at the German Cancer Research Center in Heidelberg has been given the €15,000 Endoscopic Research Award 2011.

Award-Winning Research on Childhood Brain Tumors

Dr. Stefan Pfister and Dr. Andrey Korshunov won the Fritz Lampert Award for their work on the analysis of genetic alterations in ependymoma. Dr. Hendrik Witt was distinguished with the AACR-GlaxoSmithKline Clinical Cancer Research Scholar Award for his discovery of epigenetic alterations known as methylation patterns in pilocytic astrocytoma.
New Technology Manager in the Office of Technology Transfer

Dr. Dirk Kuck recently started working in the Technology Transfer Office as project manager for the “Helmholtz Drug Research” platform. The Helmholtz Association has launched a long-term funding program across different centers to establish a combined chemical-biological platform for the development of novel and innovative drugs. Six Helmholtz centers together with external partners will now cross-link their expertise in the field of drug research. The objective is to provide high-quality targets and drug candidates for clinical applications. Dr. Kuck is responsible for the identification and coaching of appropriate projects at the DKFZ for this platform.

Dr. Kuck is a biologist and was most recently employed by Bayer in the "Tumor Biology and Translational Oncology Research" division, where he was involved in the discovery and validation of oncologic targets. Before he joined Bayer, he worked on various translational projects in the field of drug discovery in the Department of Epigenetics and in the Department of Tumor Virology on the development of HPV vaccines at the DKFZ.