CaRe2B

Cancer Research to Business
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GERMAN CANCER RESEARCH CENTER IN THE HELMHOLTZ ASSOCIATION

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EDITORIAL

Dr. Ruth Herzog

Dear colleague and business partner,

The featured opportunity in this issue is the novel VLP-vaccine against Epstein-Barr-Virus (EPV) and its inventor Henri-Jacques Delecluse. The vaccine fulfills the criteria for a vaccination strategy against EBV infection. Moreover this vaccine shows the potential to become as successful as its predecessor - the vaccine against human papilloma viruses originating from DKFZ's Nobel prize-winning research.

This October is expected to be golden, with a good harvest and great opportunities. This is evidently true for SCIOMICS, our newly formed spin-off company, which first presented at Biotechnica, Hannover, Europe's marketplace for biotechnology and life sciences. CEO Christoph Schröder reports that he has attracted many new customers for his new business. INVISTRO is DKFZ's new spin-off in the field of preclinical imaging, headed by CEO Jörg Peter (see Care2B issue 2/2012) and CFO Klaus Blettner. The founders are currently looking for investors. Have a look at these and other opportunities from the DKFZ and please do not hesitate to contact us. You have the opportunity to meet us personally at BioEurope in Vienna, on November 4-6, and at the Innovation days in Berlin, on December 11-12.

I sincerely wish you and your partners golden business days today and tomorrow!

Cheers

Ruth Herzog

E-mail: r.herzog@dkfz.de

Content:

Feedback: technologietransfer@dkfz.de
Address: Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 280, D-69120 Heidelberg, Germany,
Phone: +49 (0)6221 422958, Fax: +49 (0)6221 422956

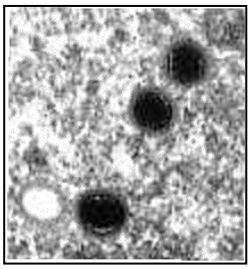
FEATURE ARTICLE

A new vaccine to prevent EBV-associated diseases including malignancies (P-989)

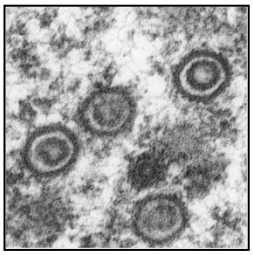
Dr. Henri-Jacques Delecluse

The Epstein-Barr-Virus (EBV, also known as Human Herpes Virus 4, HHV 4) belongs to the human gamma-herpesvirus subfamily and is associated with approximately 2% of tumors worldwide. These predominantly consist of lymphomas and carcinomas, but also include rare cases of smooth muscle tumors.

The first contact with EBV often occurs during early childhood and is usually asymptomatic. However, the virus will establish lifelong clinically silent persistence in its host. EBV infection is very efficient, and it is estimated that over 90% of adults worldwide are infected by the age of 40. If EBV infection is delayed until late teenage years, an infectious mononucleosis (IM), also known as kissing disease, can develop. IM is a self-limiting lymphoproliferative disease from which many individuals recover within 2 to 4 weeks. However, up to 10% of IM patients suffer from protracted fatigue for 6 months or longer, and approximately 1% of persons suffer additional complications such as acute hepatitis or meningoencephalitis. Individuals who have suffered an episode of IM are associated with a greatly increased risk of developing both Hodgkin's and non-Hodgkin's lymphomas. Immunosuppression, whether needed for tolerance of transplanted organs or caused by HIV infection, impairs the body's ability to control the persistent virus and often results in higher EBV loads and a higher risk of EBV-associated diseases. **Early EBV preventative vaccination could reduce EBV-associated diseases, including malignancies, and would have a substantial public health and economic impact.**



EBV wildtype



EBV mutant – virus capsid without any EBV-DNA

Professor Henri-Jacques Delecluse and his group have developed a new vaccination strategy to prevent EBV infection that is based on virus-like particles, a type of virus structure that has already been successfully used for the construction of vaccines against hepatitis B and human papillomavirus infection. Virus-like particles consist of one or two viral proteins that can reproduce more or less faithfully the structure of the mature virus, but lack its viral nucleic acids. Thus, they can elicit an immune response without being able to propagate into the infected host and cause disease. **To date, no efficient vaccine against EBV is available,** and EBV-VLP would represent attractive candidates as vaccines. However, the number of viral proteins necessary to construct EBV-VLP is so high that a new approach was needed. Therefore, the inventors obtained the **VLPs directly from EBV-infected cells**. This became possible when the **two viral proteins** BFRF1a and BFLF1 **involved in viral DNA packaging into the viruses were knocked-out** of the EBV genome. 293 cells that stably carry this defective virus produce **VLPs completely devoid of viral EBV-DNA but that are able to induce the activation of EBV-specific cytotoxic CD4-positive T-cells**. Therefore, EBV-VLPs fulfill the criteria required for the design of a vaccination strategy against EBV infection.

[Link Technology Offer]

Inventor profile

Professor Henri-Jacques Delecluse MD was trained as a pathologist specialized in hematological diseases. He joined the DKFZ in 2004 to head the division of pathogenesis of virus-associated tumors. Since last year he is also director of the research unit “Unité Inserm 1074” established by the French ‘Institut National de la Santé et de la Recherche Médicale’ (Inserm) at the DKFZ. His research interest is focused on the study of the molecular processes through which the Epstein-Barr virus causes cancer, and how this knowledge can be used to prevent these diseases though vaccination.

NEW TECHNOLOGIES

THERAPEUTICS

Antibody specifically binding the enzymatically active form of HIPK2 (P-1097)

The serine/threonine protein kinase Homeodomain Interacting Protein Kinase 2 (HIPK2) is an evolutionarily conserved regulator of cell death and cell growth. Like any other kinase it can exist in active and inactive states. To date, no modifications of HIPK2 have been identified that are suitable for predicting its kinase activity. The present invention therefore aims to provide an antibody binding only the activated form of HIPK2.

Optimized AAV Vectors for high transduction rates in eukaryotic cells (P-1054)

DKFZ inventors have identified two heptapeptide insertions which provide great advantages for AAV (Adeno-Associated Virus) vectors in transducing cells. In particular, DANN delivery to cells that are difficult to transfect or transduce is facilitated. The optimized AAV vectors can be used as a research tool, for gene therapy or vaccine development.

Therapeutic Antibody against Herpes Simplex Viruses type 1 and 2 (P-1048)

A humanized monoclonal antibody (mAb hu2c) has been developed that completely abrogates viral cell-to-cell spread, a key mechanism by which HSV-1/2 escapes humoral immune surveillance. Moreover, mAb hu2c neutralized HSV fully independently of complement and/or immune effector cell recruitment in a highly efficient manner.

Monoclonal Antibodies against HDAC11 (P-1040)

Modifications of histones are known to play a role in cancer, altering the accessibility of DNA for transcriptional processes. So there is an urgent need for detection methods for enzymes that modify histones. We established two hybridoma cell lines that produce antibodies directed against HDAC11 and are suitable for immunocytochemistry, chromatin IP, and Western Blot

Evi/Gpr177 as target and marker in tumors (P-975)

DKFZ inventors have 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 is correlated with poor prognosis. Silencing of the Evi/Gpr177 protein significantly inhibited glioma cell proliferation and migration. Additionally, an inhibitory antibody against Evi/Gpr177 has been invented that significantly reduces Wnt Evi/Gpr177 gene response.

Determination of in vivo DNA double-strand break localization and application thereof (P-907)

The technology is a method for determining the in vivo localization of double-strand breaks in a host cell, comprising a) incubating said host cell suspected to comprise DNA double-strand breaks and a linear polynucleotide comprising a known sequence, b) detecting the in vivo insertion sites of said polynucleotide in the genome of said host cell, c) determining the in vivo positions of double-strand breaks, and d) assessing the in vivo localization of double-strand breaks.]

Bone morphogenetic protein 4 (BMP4) for treating advanced stage neuroblastoma (P-804)

Specific inhibition of histone deacetylases by BMP4 efficiently restores aberrant signaling pathways and biological features in experimental neuroblastoma at nanomolar concentration without unfavorably targeting untransformed cells.

In addition, recombinant manufactured BMP4 is already established for other indications (osteoporosis and type 2 diabetes), which should support the approval for this new indication.

Peptides for inhibition of the HPV-E6 oncoprotein (P-797)

The peptides identified by our inventors block the intracellular activity of the HPV16 E6 protein and thus increase sensitivity of tumor cells towards apoptosis. This effect is highly specific for HPV16-containing tumor cells.

A list of all therapeutics can be found here [Link]

DIAGNOSTICS

Histone mutations as marker for Glioblastoma (P-1012)

This technology was achieved by a cooperation between McGill University and DKFZ. Brain tumors, such as the highly aggressive glioblastoma multiforme (GBM), are currently the leading cause of cancer-related mortality and morbidity in children. Current diagnosis of brain cancers involves MRI, PET and CT scans, angiographies, followed by biopsies performed either during the resection of the tumor or as a separate procedure via a burr hole. A blood-based test would provide a more economical, i.e. accessible and less invasive, diagnostic tool. The GBM-specific biomarker has been patented and is available for licensing, i.e. for companion diagnostics.

A list of all diagnostics can be found here [Link]

RESEARCH TOOLS

Multiple orthogonal labelling of oligonucleotides (P-1007)

Labeled oligonucleotides are used in research and for diagnostic, therapeutic and industrial applications. Researchers from the DKFZ and Heidelberg University have developed a fast method for post-synthetic multiple orthogonal labeling of oligonucleotides by combining the inverse Diels-Alder reaction with the well-known copper-catalyzed azide-alkyne cycloaddition. Advantages:

- easy, fast, and cost-effective method
- highly efficient one step reaction
- protection groups are not needed
- solvent-independent
- no chemical byproducts or side reactions

Quadscanner for High Resolution Scanning Microscopes and Array Readers (P-750)

The key facts: (1) Fast, adaptive optical scanning device; (2) Completely free positioning of the scanning mirrors regarding the conjugated back focal plane; (3) Calibration with 4 galvanometers; (4) Application in high resolution microscopes (fluorescence, Raman, STED, localization), but also in Array Readers.

A list of all research tools can be found here [Link]

DEVICES

New MLC generation for radiotherapy: drive concept leaves by using linear servo motor (P-1044)

The aim of radiation therapy is to eradicate a tumor without causing significant damage to contiguous normal tissue. Multileaf collimators (MLC) have been broadly established for precise field shaping of the radiation beam. The linear servo MLC presented here provides various advantages over conventionally employed MLCs, e.g.:

- reduced size and weight
- dynamic leaf movements up to 4 m/s
- direct fixation of the linear servo rod to the associated leaf
- position sensors are implemented in the linear drives

Measurement of protein mobility and interactions in living cells by 3PEA (P-991)

Several limitations restrict the application of conventional Fluorescence Recovery After Photobleaching (FRAP). Examples: 1) Low temporal

resolution, which prohibits measurements of faster processes 2) FRAP evaluation schemes cannot include spatial constraints imposed by the cellular environment on protein mobility 3) FRAP ignores the sequential nature of the bleaching and image acquisition process.
In order to overcome these limitations of conventional FRAP, DKFZ researchers have developed a novel FRAP based method called 3PEA (Pixel-wise Photobleaching Profile Evolution Analysis). The advantages of 3PEA include: accurate mobility measurements of fast, slow, and immobile proteins and fast determination of effective diffusion coefficients.
The presented technology is thought to be suitable for use in all confocal laser scanning microscopes (no additional hardware is needed) and would allow automated high-throughput FRAP experiments.

Compact Multileaf-Collimator with small diameter (P-901)

Currently, Multileaf Collimators (MLC) are established and state of the art in numerous devices for radiotherapy used for cancer treatment. However, the established MLC comprising 80 leaves or more require an enormous amount of space for the leaves and corresponding drive elements and position measuring/ acquisition. Since space is very limited within the head of linear accelerators, DKFZ has developed a smaller-sized Compact MLC, and testing of the corresponding prototype has proved successful.

Local Dose Shaping for Planning Treatment in Radiotherapy (P-854)

Self-assembling nanoparticles consisting of N-terminal truncated hepatitis B virus surface antigen S are able to package and deliver a multitude of agents, e.g. nucleic acids, proteins, cytotoxic drugs, siRNA. Incorporating targeting peptides into the membrane of the nanoparticles facilitates accurate agent delivery to the cells of interest. Additionally, the encapsulation of agents with unfavorable pharmacokinetic characteristics increases the availability of these agents.

Chamber for Fluorescent Microscopes (P-818)

The observation chamber consists of a main piece made out of a suitable metal, a specific seal, and a sample holder made from durable material. The choice of the circular cover slides is left to the users. A tool that is provided allows fast assembly and disassembly of the chamber. The chamber is designed for observing samples such as living cells and solutions in optical or fluorescent microscopy, and also for use with all techniques requiring an observation chamber with a glass bottom. It provides an inexpensive way to observe and measure cells or samples in comparison to "throw-away" or "high-end" solutions, particularly if large numbers of observations are involved. The design is technically simpler than competing products and can therefore be marketed at a low price.

FAM: Fluorescence Activation Microscopy, a new Principle for 3-Dimensional Fluorescence Microscopy (P-803)

FAM enables optical sectioning without necessarily requiring confocal optics or 2-photon excitation.
Axial signal discrimination is generated by the illumination beams alone. If activation microscopy is combined with confocal or 4Pi optical setups, optical probe volumes below 1 attoliter can be achieved. Furthermore, fast CCD camera detection is enabled with axial discrimination comparable to confocal and 2-photon setups. When used together with fluorescent proteins such as DRONPA, fast 3d live cell imaging becomes possible.
FAM suppresses the side-lobes in 4Pi microscopy by a factor of at least 3 in very much the same way as in 2-photon excitation, which actually brought about the breakthrough in high resolution 3d microscopy with two opposing micro-objectives. The axial resolution is improved down to less than 70nm by purely physical means. Furthermore, the integrated effective detection volume is decreased 4-fold.
The point spread function calculations presented suggest that activation-supported fluorescence may perfect other high resolution imaging techniques such as STED and PALM additionally by the introduction of an axial resolution in the 70nm range.

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

VACCINES

A new vaccine to prevent EBV associated malignancies (P-989)

See feature article

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

SOFTWARE

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. For this purpose, the pose of the mobile device, which represents the viewing direction of the user, is continuously estimated by registering (i.e., aligning) the ToF data acquired during the visualization process with the patient surface extracted from the 3D medical data set. During

camera pose estimation, a custom-designed algorithm accounts for the camera-specific localization errors.

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

PATENTS GRANTED

Since the last issue of the newsletter, 6 patents have been granted, all of which are licensed exclusively to DKFZ industry partners

NEW AND NOTABLE

Licencing agreement for high-resolution images in medical research

STED microscopy creates high-resolution images far below the diffraction limit of visible light. However, the technique's engineering aspects remain comparatively complex, which impedes its dissemination and use. A technology called EASYDOnut, developed by the German Cancer Research Center and the Max Planck Institute for Biophysical Chemistry, simplifies the optical system considerably and has now been licensed by spin-off Abberior GmbH.

Black sheep in the family: Why some infections with the Epstein-Barr virus cause cancer

Epstein-Barr viruses (EBV) are very common around the world; almost everybody is infected. In most cases, an infection causes no harm, but sometimes the outcome is a serious disease. EBV may lead to infectious mononucleosis (Pfeiffer's disease), which is common in Germany; in other parts of the world it even causes cancer. The reasons why EBV infections follow such diverse courses have been unclear. But now scientists from a team headed by Henri-Jacques Delecluse at the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) have discovered that Epstein-Barr viruses occur in various strains that differ in terms of their aggressiveness. These findings are extremely important both for finding strategies to fight the diseases caused by EBV and for developing vaccines against infections with the virus.

SPIN-OFFS

Sciomics – Antibody meets microarray

Sciomics GmbH was founded in spring 2013 as a spin-off company of the German Cancer Research Center (DKFZ). The company is specialized in the development of antibody microarrays for customized antibody microarrays, dedicated antibody arrays for pathways as well as diseases and service analysis. Using antibody microarrays it is possible to analyze complete signaling pathways, upstream/downstream elements of a customer's protein of interest or hits from next generation sequencing on their impact on protein level. For such an analysis only very small sample volumes as low as 15µL of plasma are needed. This facilitates a robust and multiplex analysis of plasma or tissue proteins not only from human but also from murine samples. Sciomics GmbH is based in Heidelberg, Germany.

Invistro GmbH - High Class Innovative Optical Instruments

Invistro GmbH was founded in July 2013 as a spin-off project at German Cancer Research Center (DKFZ). Invistro's shareholders are Dr. Jörg Peter (CEO, (co)inventor of all Invistro instruments), Professor Klaus Blettner MD (CFO) and DKFZ.

Invistro GmbH develops and produces highly innovative optical instruments for preclinical synchro-modal diagnostic imaging. Base product is a patented imaging device that is being used for high-throughput monitoring of functional and molecular processes in vivo via the detection of light photons as emitted from bioluminescent or fluorescent imaging probes. As the base technology has been developed specifically to be fully compatible with all major imaging modalities (PET, SPECT, CT, MRI), a complete portfolio of dedicated Invistro instruments can be offered to the customer for seamless integration into secondary imaging systems. For the first time, this enables three-dimensional optical data to be acquired within the anatomical context in only one imaging procedure and/or intermodal optical data to be acquired simultaneously, e.g. monitoring of fused optical and radioactive signals.

Affimed subsidiary Amphivena Therapeutic Inc. raises US$ 14 million funding

Together with the London Innovation Centre of Johnson & Johnson and Janssen Research & Development, Amphivena will use the funding for the development of bispecific antibody drugs for blood cancer based on the TandAb technology platform. Amphivena Therapeutic Inc. was founded six month ago in the US state of Delaware and is a subsidiary of the DKFZ spin-off Affimed.

AWARDS

Harald zur Hausen elected into the First Class of the Fellows of the American Association for Cancer Research Academy

The American Association for Cancer Research inaugurated the first class of the Fellows of the AACR Academy at the AACR Annual Meeting 2013, held in Washington, D.C., April 6-10. Among the first fellows is Nobel laureate Harald zur Hausen, former Scientific Director of the German Cancer Research Center in Heidelberg.

Felix Burda Awards for Commitment to Colorectal Cancer Screening Presented to Researchers from DKFZ and NCT

The Felix Burda Awards were presented for the eleventh time on Sunday, April 14. The award in the category “Medicine and Science” went to Dr. Christian Stock, Dr. Michael Hoffmeister and Professor Hermann Brenner of the German Cancer Research Center (DKFZ). The award in the new category “Best Prevention Idea” was given to Cornelia Ulrich, Dr. Ulrike Bussas and Clare Abbenhardt of the National Center for Tumor Diseases (NCT) Heidelberg.

Disrupted Lipid Metabolism: Young DKFZ Researcher Honored with Two Awards

Molecular biologist Dr. Maria Rohm pursues research on fat decomposition in the human body. Now she has won two prestigious awards at once for her research: the Novartis Young Endocrinologist Award, worth €10,000, of the German Society of Endocrinology (DGE), and the €7,500 sponsorship award of the German Diabetes Association (DDG), donated by Sanofi-Aventis Germany. Maria Rohm works as a scientist at the German Cancer Research Center (DKFZ), where she is studying the molecular foundations of a disrupted lipid metabolism.

High Distinction for Heidelberg Neuroradiologist

Dr. Alexander Radbruch has been honored with the Coolidge Award granted by GE Healthcare for his work on the use of new imaging techniques in brain cancer diagnostics. He leads the research group “Neuro-oncologic Imaging” at Heidelberg University Hospital and the German Cancer Research Center (DKFZ).

Prof. Dr. Wolfgang Schlegel nominated as outstanding contributor to the advancement of medical physics over the last 50 years

To mark the 50th Anniversary of the International Organization for Medical Physics (IOMP), national and regional medical physics organizations were

invited to nominate medical physicists who have made an outstanding contribution to the advancement of medical physics and healthcare through research, clinical developments, education and training activities, service development, and to professional matters over the last 50 years.