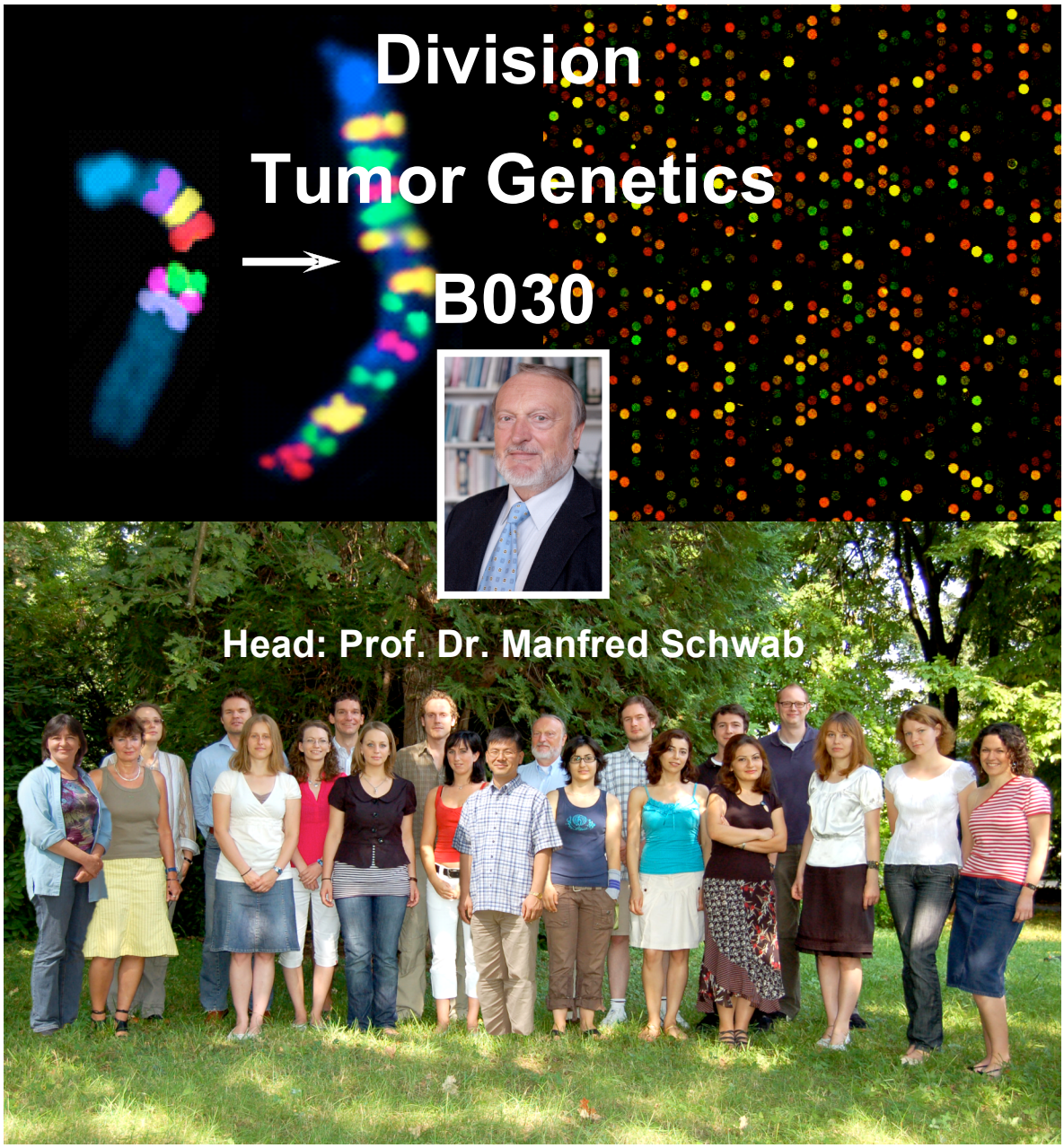

A full-color version is at: http://www.dkfz.de/de/tumor-genetics/index.html

Scientific report and 5-year future perspective

Introduction

The division is focused on two areas of active research. One, basic and translational aspects of the major pediatric solid cancer, neuroblastoma. And two, the FRAGILOME project, which aims at deciphering the set of genes at predetermined chromosome breakage sites (common fragile sites, cFS) of the human genome, define their functions and explore which of the genes can undergo genetic damage as the result of cFS activation and consequently contribute to tumorigenesis.

Neuroblastoma is the most frequent single-entity solid cancer in young children. Over the last 20 years, research activities have tremendously increased worldwide, and neuroblastoma has become an increasingly attractive tumor model. Accordingly, the neuroblastoma community, as judged by the number of scientific publications, but also by the presence of scientists at bi-annual meetings on "Advances in Neuroblastoma Research" (http://www.anrmeeting.org/index.shtml) has grown from a small number to a large scientific community. In spite of the tremendous progress in understanding neuroblastoma development, the prognosis of patients, particularly those with advanced disease, has remained dire. The phenotype of spontaneous regression in a subset of approximately 10% of neuroblastomas is under vigorous investigation in our laboratory, as understanding the pathways leading to regression could be a point of departure for developing new anti-neuroblastoma therapies.
The attraction of numerous scientists to study neuroblastoma, which is considered a rare tumor, to large extent has been fueled by two principle discoveries. One, neuroblastoma had been the first tumor for which parallel (array) analysis had been used for mRNA expression profiling. And second, by using array profiling, the very first onco-genetic biomarker had been identified, the amplified *MYCN* gene, which today is in successful clinical use worldwide for neuroblastoma therapy design. In addition, extensive biochemical and molecular analyses by our group have demonstrated that the enhanced expression of the MYCN-protein, consequent to gene amplification, occupies a central role in the development of at least a subset of neuroblastomas.

The Divison of Tumor Genetics is internationally well positioned as one of the leading groups on basic and translational aspects of neuroblastoma research. This is mainly documented by the highly-reviewed national and international research networks, which have been and are being coordinated by this Division. Additional strength has come from the close collaboration, with full spatial integration of laboratories, with the DKFZ-Children's Clinic Heidelberg Clinical Cooperation Unit (G340; Head: Professor Olaf Witt) addressing neuroblastoma with emphasis on a translational perspective.

Main achievements over the past 5 years include

- Assembly of a diagnostic NB chip and introduction into the clinic. We have developed a designer diagnostic NB chip that significantly outperforms all currently used neuroblastoma risk stratification systems. From February 2008, this diagnostic NB chip has become part of the clinical German NB trial protocol and is currently included in a

feasibility study by the US FDA. To our knowledge this is the first gene expression-profiling tool that has been integrated into a nationwide clinical cancer trial.

- Molecular definition of spontaneous NB regression. We have established the first model of spontaneous NB regression, which is based on a low-level MYCN-protein function gain in NB cells. Based on this model, we are currently studying new therapeutic concepts using selective small compound inhibitors targeting defined *MYCN* oncogenic functions that are exclusively deregulated in high-risk neuroblastomas, such as MDM2, CDK4 and HDAC deregulation.

- Dissection of MYCN and c-MYC function in NB tumorigenesis. We have identified several new candidates genes, such as SOXN, ATXN2, CTSD, SKP2, through which MYC proteins control the different cellular NB phenotypes.

- Identification of *CAMTA1* as a new tumor suppressor gene on chromosome 1p36. Allelic loss at distal 1p is a common feature of neuroblastomas and various other tumors. Ectopic induction of this gene inhibits features of aggressive cancer cells and induces neuronal differentiation.

The **FRAGILOME project** has been started more recently. As a background information, the human genome contains approximately 120 predetermined DNA breakage regions, referred to as common fragile sites (cFS) that have been cytogenetically mapped to specific sites existing on basically all chromosomes. cFS should not be confused with rare FS (rFS), such a “fragile-X”, which in contrast to cFS do not involve DNA breakage. The rFS merely represent a constriction of a chromosomal region, consequent to abnormal expansion of trinucleotide repeats, and there is no evidence for their involvement in human malignancies. Activation of cFS, and thereby DNA breakage, can occur as the consequence of DNA-replication stress, such as by certain chemicals, e.g. acting as DNA polymerase inhibitors. While DNA breaks can be repaired, this often involves a reduced fidelity with the consequence of persisting DNA changes. One major gross chromosomal alteration departing from cFS activation is DNA amplification, which is a major type of chromosomal change in cancer cells. Neuroblastoma provides the prototypic example for a role of amplification in tumorigenesis. From this it would follow that cFS should represent a productive source from which further insight into genomic changes in tumorigenesis can be derived. Little attention has been given in the past to identify which of the cytogenetically mapped cFS might encompass one or several genes that may be damaged consequent to cFS activation. However, it should be obvious that cFS represent risk regions in the human genome from which genomic damage preferentially can depart.

The strategic aim of the FRAGILOME project is to systematically explore the genetic information of the repertoire of cFS, characterize the core regions of cFS DNA breaks, define persisting cFS gene damage and explore in which way the damaged genetic information might contribute to tumorigenesis. In perspective, it will be tested if such damaged genetic information could be used as a biomarker for clinical management or even as a therapeutic target.

Main achievements over the past 5 years include the

- Establishment of a strategy for mapping cFS genes by a combination of FISH (using YAC and BAC probes) and by intelligent bioinformatics for gene identification.

- Identification of the genomic architecture and informative content of close to 20 previously uncharacterized cFS.

- Design of Fine Tiling CGH chips for exploring genomic damage of cFS genes in human tumor samples.

- Documentation of the significance of cFS for oncogene amplification, determination of the origin of *MYCN* amplification from cFS *FRA2C.*

- Demonstration that haploinsufficiency of the breast cancer risk gene *BRCA2* results in a hypersensitivity to conditions that provoke replication stress, determination of breakage at cFS *FRA9G* in *BRCA2*-associated high risk breast cancer patients leading to disruption of the *C9orf39* gene, with as yet unknown function.

Description of past and ongoing projects, 5-Year Future Directions

1. Neuroblastoma

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1.1. NB diagnostic chip in the clinic

Clinical courses of neuroblastomas are highly variable ranging from spontaneous regression to relentless progression. Accordingly, treatment intensities range from a wait-and-see strategy to intensive multimodality therapies making risk prediction at the time of diagnosis an important task. Current risk stratification systems that are based on clinical, histomorphological and genetic markers, including amplified *MYCN* oncogene and deletion of chromosome 1p material are still error prone, particularly for neuroblastomas that lack amplified *MYCN* oncogene. To develop a robust risk stratification tool based on gene expression data, all key genetic determinants dictating neuroblastoma phenotypes should be adequately represented on such a diagnostic tool. In a collaborative effort within the **G**erman **R**esearch **A**ssociation for **N**euroblastoma **T**argeted **T**herapies (GRANT funded by NGFN2), we have gathered gene expression data from a large set of neuroblastoma tumors using different high-throughput gene expression analysis tools: standard expression arrays, customized arrays based on subtractive cDNA libraries and SAGE libraries were used to define a comprehensive list of genes reflecting the expression repertoire of individual neuroblastoma phenotypes. In addition, transcripts mapping to frequently altered chromosomal regions were included. Based on this unique compilation of neuroblastoma phenotype-specific transcripts, we designed a customized microarray consisting of 10.163 oligos representing 8.155 Unigene clusters and more than 2.000 newly designed probes for transcripts that were not covered by current “whole-genome” arrays. This diagnostic NB chip has been incorporated February 2008 into the clinical German NB trial protocol. Prior to this, we have

Fig. 1: Diagnostic neuroblastoma chip.

retrospectively analyzed more than 250 primary neuroblastomas. In addition, a prospective study has been established that started October 2004 to further assess the validity of this NB chip. Together, results from these two studies clearly revealed that risk prediction using this NB chip outperforms all currently used risk stratification systems.

Ongoing projects and future directions

The enormous dataset generated from primary neuroblastomas reflecting the full spectrum of biological and clinical subtypes (current status: > 500 neuroblastomas, > 1000 profiles) is currently being evaluated by an FDA-initiated quality control network (MAQC2 project, http://edkb.fda.gov/MAQC/) with the aim of establishing robust standards for the transfer of high-throughput gene expression tools and classifiers into the clinic. To further evaluate the usefulness of the diagnostic NB chip as a risk stratification tool, we have collected additional neuroblastoma specimens from partners within the EU. For this and for the elucidation of shared altered molecular pathways in embryonal tumors, we have set up the EET- (European Embryonal Tumor) Pipeline consortium, funded by the Sixth Framework Program of the EU.

1.2. Spontaneous NB Regression: A Goldmine for New Therapeutic Concepts

Spontaneous regression of metastatic neuroblastoma disease occurs in approximately 10% of neuroblastomas (stage 4s *MYCN* non-amplified tumors). By analyzing spontaneous regressing as well as progressing tumors at the mRNA and DNA level using different high-throughput technologies, we established the first model of spontaneous neuroblastoma regression in stage 4s neuroblastomas that is based on a low-level function gain of the MYCN oncoprotein. In contrast, progressing neuroblastomas showed highly deregulated activity of either MYCN or c-MYC. Based on this findings, we designed new therapeutic concepts that use selective small compound inhibitors targeting defined MYCN/c-MYC functions that are exclusively deregulated in high-risk neuroblastomas, such as MDM2 and CDK4 activation. Furthermore, to identify small compounds that inhibit MYCN/c-MYC functions in high-risk neuroblastomas, we searched for drugs that suppresses the gene expression signature triggered by highly deregulated MYCN or c-MYC. Several HDAC inhibitors were among the top-ranked drugs suppressing the MYCN/c-MYC-regulated gene expression signature in neuroblastoma cells *in vitro*. With the toxine of the fungus *Helminthosporum carbonum* (HC-Toxin), we identified an HDAC-inhibitor leading to induction of differentiation, inhibition of proliferation and cell cycle, as well as induction of apoptosis in neuroblastoma cells (including *MYCN*-amplified cells) at nanomolar concentrations. Most intriguingly, the novel drug has no effects on proliferation, morphology or apoptosis of normal fibroblasts in this concentration

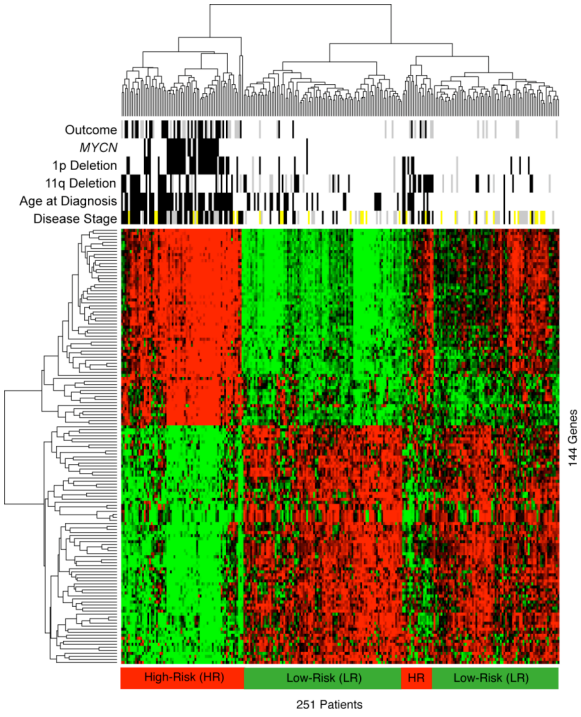

Fig. 2: Gene expression profiling distinguishes progressing and regressing neuroblastomas. Regressing stage 4s tumors are marked in yellow (disease stage) within the low-risk group (green).

range. We therefore anticipated a tumor-selective effect and protected the HC-Toxin by a patent (PCT/EP2007/061206).

Ongoing projects and future directions

Ongoing and future work focuses on the translation of these new therapeutic concepts into the clinic. Prior to this, extensive *in vivo* testing using NB mouse models will be performed (funded by NGFN^{Plus}).

1.3. Dissecting MYCN and c-MYC functions in tumorigenesis and in neuroblastoma-initiating (stem) cells

Enhanced activity of MYC transcription factors, such as MYCN and c-MYC, contributes to almost every aspect of tumor formation: unrestricted cell proliferation, inhibition of differentiation, cell growth, angiogenesis, reduced cell adhesion, metastasis, and genomic instability. In line with this, MYC proteins are thought to play a crucial role in cancer-initiating (stem) cells. In contrast, MYC proteins also sensitize cells for apoptosis, a function that should inhibit tumor formation. The full spectrum of target genes through which MYC transcription factors mediate these contrasting functions is still unclear. We have used different functional approaches to elucidate pro-tumorigenic or pro-apoptotic MYCN and c-MYC functions in neuroblastoma cells. (1) A function-based gene cloning approach based on the "Technical Knock Out" (TKO) strategy was used to identify death-associated genes due to their inactivation by antisense RNAs expressed from an episomal cDNA library. Using this approach and validated by siRNA technology, we established *SOXN* and *ATXN2* as new candidate genes through which MYCN controls pro-apoptotic activities in neuroblastoma cells. As a pro-survival signal in chemo-resistant neuroblastoma cells with deregulated *MYCN*, we identified *CTSD,* a new target of MYCN in neuroblastoma cells. (2) In addition, we used a reverse genomics approach to identify pro-tumorigenic functions of MYCN and c-MYC in neuroblastoma cells. For this, we generated gene expression profiles from a neuroblastoma culture model that allows conditional activation of either MYCN or c-MYC to define MYCN/c-MYC oncogenic signatures. Mapping these oncogenic signatures from the *in vitro* system to gene expression profiles of primary neuroblastomas, we identified Skp2, the SCF ubiquitin ligase controlling p27 functions, as a crucial downstream component of deregulated MYCN/c-MYC in high-risk neuroblastomas.

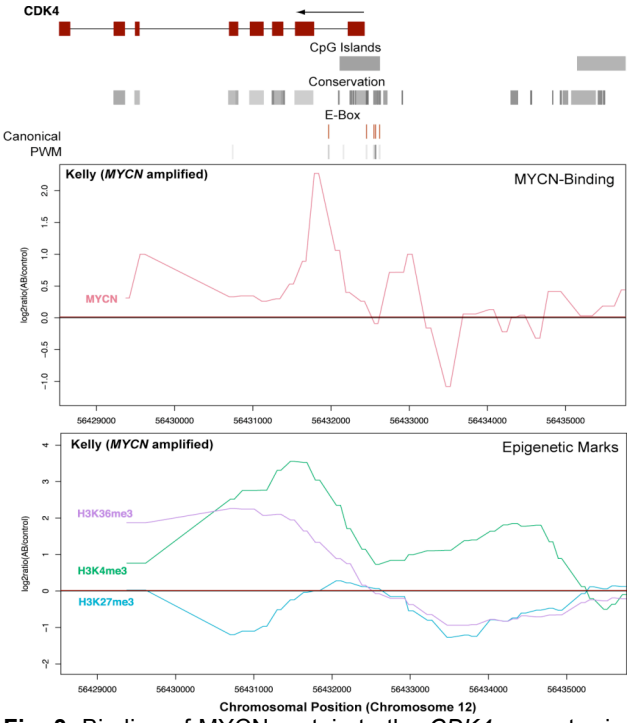

Fig. 3: Binding of MYCN protein to the *CDK4* promoter in *MYCN* amplified neuroblastoma cells (Kelly) as measured by Chromatin Immunoprecipitation (ChIP)-chip. Different epigenetic marks associated with active transcription (H3K4me3), elongation (H3K36me3), and repression (H3K27me3) allow for the distinction of actively transcribed and repressed genes.

Ongoing projects and future directions

Current projects use Chromatin Immunoprecipitation (ChIP-chip as well as ChIP-sequencing) to further dissect MYCN and c-MYC functions in neuroblastoma cells from different neuroblastoma subtypes, including neuroblastoma-initiating (stem) cells. MYCN- and c-MYC binding to target gene promoters is analyzed in different cell types together with epigenetic markers that allow the distinction between activated and repressed genes. Within the EET (European Embryonal Tumor) Pipeline consortium funded by the EU, we are also analyzing MYCN and c-MYC functions in other embryonal tumors. In addition, our functional approaches to dissect MYCN/c-MYC functions will be further expanded to a whole genome siRNA screen for neuroblastoma disease-relevant genes using reverse transfections on cell arrays, funded by the NGFN^{Plus}.

1.4. *CAMTA1*, a new tumor suppressor gene on chromosome 1p36

Allelic loss at distal 1p is a common feature of neuroblastomas and various other tumors, and it is widely assumed that this region harbors genetic information relevant for development of these malignancies. For almost two decades numerous studies have attempted to refine the complexity of the 1p deleted region in order to increase the chances for identifying the gene(s) of interest. Using loss of heterozygosity studies, we considerably narrowed down the region deleted in neuroblastomas, allowing for the first time to pinpoint single genes. Extensive sequence analysis of all candidate genes revealed tumor-specific sequence variants in the transcription factor gene *CAMTA1*. The potential influence of these variants on tumorigenesis is currently under investigation.

Integrating global microarray expression data and clinico-biological parameters revealed that low expression of *CAMTA1* mRNA is significantly associated with poor neuroblastoma outcome. The robustness of this marker could be confirmed via QPCR in a large independent patient cohort. Intriguingly, multivariate analysis revealed that the prognostic information of *CAMTA1* expression was independent of all tested established risk markers, including 1p deletion. These data suggest that (i) *CAMTA1* expression represents a new powerful prognostic variable, which will improve current risk stratification models for neuroblastoma (ii) *CAMTA1* is a strong candidate for the 1p gene being involved in the development of neuroblastoma and other tumors. The prognostic significance of *CAMTA1* expression could be confirmed by other US-american and european groups and was recently extended to other tumor entities like colorectal cancer.

We further assessed the functional role of *CAMTA1* in neuroblastoma via establishment of CAMTA1-inducible neuroblastoma cell models. Targeted induction of this gene inhibits features of aggressive cancer cells like hyperproliferation and anchorage independent growth. Morphologically, CAMTA1-induced neuroblastoma cells exhibit features of neuronal differentiation.

CAMTA1 is a Ca^{2+}/calmodulin regulated transcription factor with its target sequences being largely unknown. To identify downstream effectors mediating CAMTA1 functions, time-resolved transcriptome profiles of two CAMTA1-induced neuroblastoma cell models were taken employing a whole genome microarray platform. Profile analysis revealed significant induction of cell cycle regulative genes and initiation of a neuronal differentiation program.

Ongoing projects and future directions

So far, chromosomal rearrangements were not found, rare *CAMTA1* sequence variants were detected. Future studies will be directed to search, by custom-designed fine-tiling CGH

arrays, for microdeletions or rearrangements on the exon level that may contribute to neuroblastoma development. These “ultra high resolution chips” allow detection of rearrangements with a resolution of less than 500 bp. After analyzing a comprehensive set of neuroblastomas, further tumor entities characterized by 1p deletion will be included.

To further shed light on the CAMTA1 regulatory network and to identify additional components of diagnostic/therapeutic relevance, we are following a computer model based approach aiming at the identification of key nodes connecting CAMTA1 to central cellular decisions. The time-resolved genome wide expression profiles of CAMTA1-induced cells will be used to build the topology of the CAMTA1-regulated network. In an iterative process predictions made by the resulting *in silico* model will be tested *in vitro* via RNAi knock-down experiments in CAMTA1 cell systems to further refine the predictive performance. Superimposing the final CAMTA1-network model onto genome wide expression data from neuroblastomas with integration of the respective clinico-biological patient features should reveal therapeutically relevant structures.

2. Fragilome Project

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2.1. Cloning and mapping of cFS gene(s)

Approximately 120 cFS have been cytogenetically identified, but for only very few the DNA damage regions or gene(s) have been determined. We are using two strategies for the identification of cFS gene(s): genetically tagging DNA by insertional mutagenesis and FISH mapping. The first molecular approach is based on the preferential integration of an exogenously supplied marker-tag into cFS regions and subsequent cloning of DNA flanking the tag. The second approach is six-colour FISH with YAC and BAC probes each labelled with different fluorescence-conjugated nucleotides (Fig.1). The simultaneous use of six different DNA probes allowed us to narrow down the region of fragility from several megabases to the exact genomic region spanning a break in each metaphase. Combining the the approaches we have identified the genomic architecture and genetic information at 17 previously uncharacterised cFS associated with cancer and other human chronic disorders (Table 1).

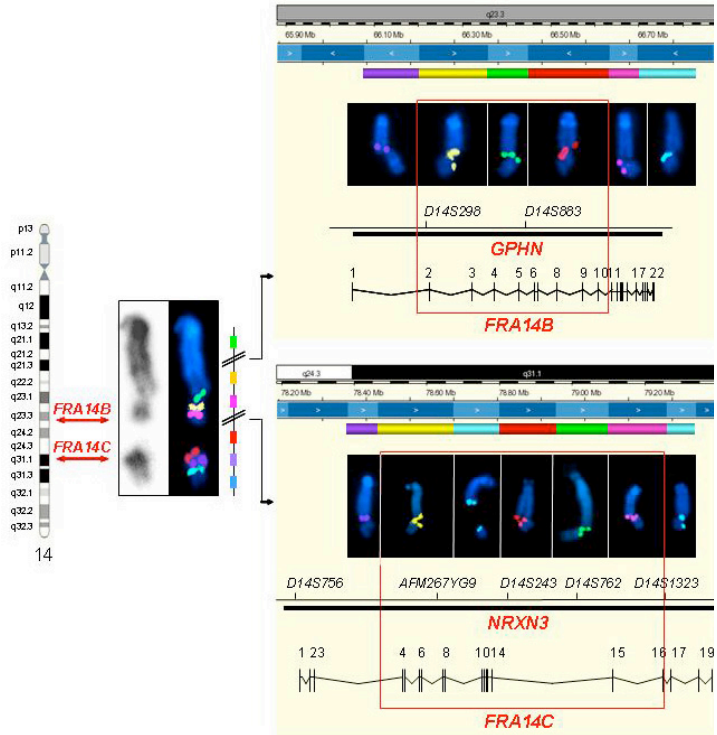

Fig. 1: Simultaneous hybridization of contiguous six-color BAC FISH allows to detect gene(s) disrupted by the activation of cFS. *GPHN* at *FRA14B*. and *NRXN3* at *FRA14C*.

Future directions

We will continue to identify the genetic information encompassing cFS. Several cFS genes, like *DAB1* (FRA1C), *CENTG2* (*FRA2J*), *NBEA* (*FRA13A*), *GPHN* (*FRA14B*), *NRXN3* (*FRA14C*) are now considered candidates for the development of non-malignant neuronal diseases, such as autism. We are going to determine whether genomic damage resulting

from cFS activation is associated with the pathogenesis of neuro-developmental disorders and/or cancers. A primary target of our interest will be to explore the genetic complexity of newly identified cFS genes and their role in tumor initiation and progression.

Table 1. New 17 fragile sites identified through *FRAGILOME* research

Fragile site	Gene	Clinical phenotype
Carcinogenesis		
FRA13D	*GPC5* (glypican 5)	amplification in lymphoma
FRA2C	*MYCN, DDX1,NAG*	amplification in neuroblastoma
FRA2I	*PARD3B*	invasive and metastatic potential
FRA3A	*RBMS3*	*c-MYC* regulation protein
Neuronal genes		
FRA13A	*NBEA* (neurobechin)	candidate gene for autism
FRA14C	*NRNX3* (neurexin 3)	candidate gene for autism
FRA2J	*CENTG2* (centaurin)	candidate gene for autism
FRA14B	*GPHN* (gephyrin)	hyperexplexia
FRA1C	*DAB1*	
FRA2E	*EXOC6B*	
Various function		
FRA1E	*DPYD*	thymine-uraciluria, fluorouracil toxicity
FRA5H	*PDE4D*	ischemic stroke
FRA9G	*C9orf39*	9p-deletion syndrome
FRA11G	several genes	
FRA6H	several genes	
FRA13E	several genes	
FRA2D	no genes	

2.2. Genomic rearrangements of cFS genes(s) in tumor cells

The activation of cFS appears to be a prominent initiating event in the generation of DNA damage, particularly of DNA deletions and DNA amplifications. For detection of genomic damage of cFS genes in human tumor cells, we are using two major approaches. Structural chromosomal rearrangements within cFS genes resulting from incorrect joining of DNA segments, such as translocations, insertions or inversions, are determined by FISH. Genetic aberrations leading to loss or gain (amplification) of chromosomal material are determined by Fine-Tiling Array CGH. Combination of both approaches allows the determination of breakpoints at ultrahigh resolution in DNA targets located within cFS and may pinpoint genomic regions harboring genes important for tumor initiation or progression. Our recent studies have shown that the amplification

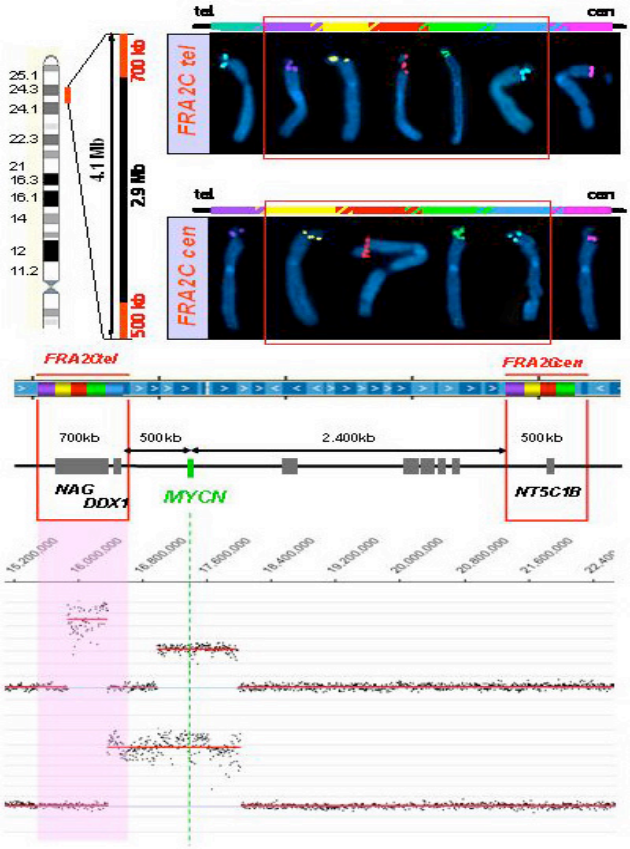

Fig. 2: *FRA2C* sequences surrounding the *MYCN* oncogene. Fine tiling microarrays on neuroblastoma cells identify chromosomal breakpoints of *FRA2C*, from which *MYCN* amplification has departed.

of the *MYCN* gene has originated from cFS *FRA2C*, which provides a prominent example for the role that cFS activation has for oncogene amplification (Fig. 2).

Future directions:

We will continue our efforts to identify genomic damage of all cFS genes that we will newly discover in the course of our cloning and mapping efforts (2.1). Particular emphasis will be on 3 tumor entities: Neuroblastoma, Breast Cancer and Colon Cancer, for which we already have a substantial set of patient materials with clinical patient information.

In particular, the assembly and use of a Fine Tiling CGH array targeting cFS sequences should provide the possibility for high though-put analyses of larger numbers of tumor samples. Any identified recurrent cFS-gene alterations will be analysed against available patient clinical data to find out if they would represent a clinically informative biomarker. In addition, we will aim at identifying the possible role that the altered genetic information might have for tumorigenesis.

2.3. Haploinsufficiency for *BRCA2,* cFS expression, and breast cancer

We have made the original observation that that mono-allelic inactivation of the breast cancer risk gene *BRCA2*, a gene required for homology-directed repair of double-strand DNA breaks, is associated with decreased ability of the cell to maintain genomic stability. We found that heterozygous *BRCA2* mutation carriers exhibit a high degree of constitutional instability in the distal portion of the short arm of chromosome 9 (distal 9p), consisting of DNA duplications, inversions, and deletions (Fig.3). The molecular basis for the instability of this chromosomal region in breast cancer patients appears to be the consequence of the activation of a newly identified cFS, *FRA9G*. Heterozygous carriers of *BRCA2* mutations exhibit an almost 7-fold increase of breakage compared to non-mutation carriers from the same families and to unrelated healthy individuals. These data support the idea that haploinsufficiency for *BRCA2* results in a hypersensitivity to conditions that provoke replication stress. We determined that breakage at *FRA9G* leads to disruption of the *C9orf39* (chromosome 9 open reading frame 39) gene, whose function is currently unknown.

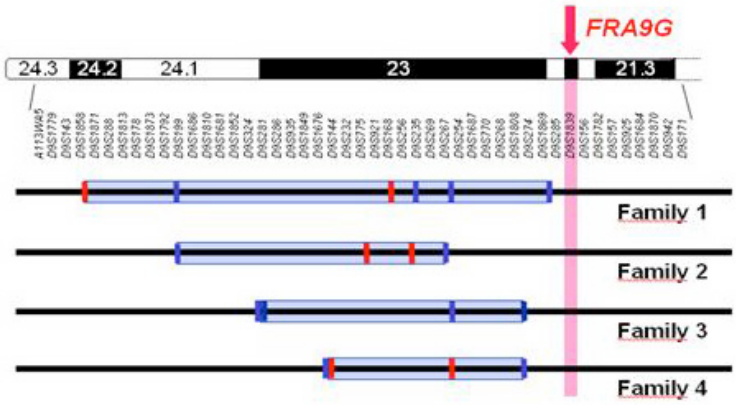

Fig. 3: Genomic regions of constitutional instability in the distal portion of the short arm of chromosome 9 (distal 9p) in four *BRCA2* mutation families. *FRA9G* is localized in a close vicinity of these regions.

Future directions:

We will analyse the function and expression of *C9orf39*. These studies will elucidate the possible contribution of *C9orf39* to tumorigenesis and, in particular, the possible role to breast cancer risk of *BRCA2* germline mutation carriers.

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[22] Savelyeva. L., Sagulenko, E., Schmitt, J.G. and Schwab, M. (2006) The neurobeachin gene spans the common fragile site *FRA13A*. Hum. Genet. 118, 551-558.

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[25] Suspitsin, E.N., Sokolenko, A.P., Togo, A.V., Lazareva, Y.R. Turkevich, E.A., Matsko, D.E., Henrich, K.-O., Borresen-Dale, A.-L., Schwab, M. Cornelisse, C.J. and Imyanitov, E.N. (2006) Nonrandom distribution of oncogene amplifications in bilateral breast carcinomas: possible role of host factors and survival bias. Int. J. Cancer 120, 297-302.

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development of a peptide (p160) with affinity for neuroblastoma cells. J. Nucl. Med. 47, 981-988.

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[35] Paffhausen, T., Schwab, M. and Westermann, F. (2007) Targeted *MYCN* expression affects cytotoxic potential of chemotherapeutic drugs in neuroblastoma cells. Cancer Letters 250, 17-24.

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[39] Sawinska M, Schmitt J.G, Sagulenko E, Westermann F, Savelyeva L. and Schwab M. (2007) Novel-aphidicolin inducible common fragile site FRA9G maps to 9p22.2, within the c9orf39 gene. Genes, Chromosomes Cancer 46, 991-999.

[40] Sagulenko, E., Savelyeva, L., Ehemann, V., Sagulenko, V., Hofmann, W., Arnold, K., Claas, A., Scherneck, S. and Schwab, M. (2007) Suppression of polyploidy by the BRCA2 protein. Cancer Letters 257, 65-72.

[41] Warnat, P., Oberthuer A., Fischer M., Westermann, F., Eils R. and Brors B. (2007) Cross-study analysis of gene expression data for intermediate neuroblastoma identifies two biological subtypes. BMC Cancer 7, 89-95.
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[44] Deubzer, H.E., Ehemann, V., Westermann, F., Heinrich, R., Mechtersheimer, G., Kulozik, A.E., Schwab, M. and Witt, O. (2008) Histone deacetylase inhibitor Helminthosporium carbonum (HC)-toxin suppresses the malignant phenotype of neuroblastoma cells. Int. J. Cancer 122, 1891-1900.
[45] Afanasyeva, E.A., Hotz-Wagenblatt, A., Glatting, K.H. and Westermann, F. (2008) New miRNAs cloned from neuroblastoma. BMC Genomics 9, 52.
[46] Nowacki, S., Skowron, M., Oberthuer, A., Fagin, A., Voth, H., Brors, B., Westermann, F., Eggert, A., Hero, B., Berthold, F. and Fischer, M. (2008) Expression of the tumour suppressor gene CADM1 is associated with favourable outcome and inhibits cell survival in neuroblastoma. Oncogene 27, 3329-3338.
[47] Sagulenko, V., Muth, D., Sagulenko, E., Paffhausen, T., Schwab, M. and Westermann, F. (2008) Cathepsin D protects human neuroblastoma cells from Doxorubicin-induced cell death. Carcinogenesis. In press.
[48] Nevo, I., Sagi-Assif, O., Botzer, L.E., Amar, D., Maman, S., Kariv, N., Leider-Trejo, L.E., Savelyeva, L., Schwab, M., Yron, I. and Witz, I.P. (2008) Generation and characterization of novel local and metastatic human neuroblastoma variants. Neoplasia. In press.
[49] Praml, C., Schulz, W., Claas, A., Mollenhauer, J., Poustka., A., Ackermann, R., Schwab, M. and Henrich, K.-O. (2008) Genetic variation of Aflatoxin B1 Aldehyde Reductase Genes (AFAR) in human tumour cells. Cancer Letters. In press.
[50] Westermann, F., Muth, D., Benner, A., Bauer, T., Henrich, K.-H., Oberthür, A., Brors, B., Beissbarth, T., Vandesompele, J., Pattyn, F., Hero, B., König, R., Fischer, M. and Schwab, M. (2008) Distinct transcritptional N-MYC and c-MYC activities are associated with spontaneous regression or malignant progression in neuroblastomas. Genome Biology. In press.
[51] Oberthür, A., Kaderali, L., Kahlert, Y., Hero, B., Westermann, F., Berthold, F., Brors, B., Eils, R. and Fischer, M. (2008) Sub-classification and individual survival time prediction from gene-expression data of neuroblastoma patients using „CASPAR“. Clin. Cancer Res. In press.

Reviews

[1] Schwab, M. (2003) Modifikationsgene bei Brustkrebs, Krebsforschung Heute.
[2] Schwab, M. (2005) Molecular Cytogenetics, In: Nai-Kong V. Cheung and Susan L. Cohn (Eds.), Neuroblastoma, Springer Verlag, pp. 27-40.

[3] Schwab, M. (Ed.). (2006) FRAGILOME – Fragile sites, genetic instability and cancer. Cancer Letters 232, 1-122.
[4] Eggert, A. and Schwab, M. (2007) Bösartigem Kinderkrebs Neuroblastom auf der Spur. GenomXPress Sonderausgabe 2, 14-17.
[5] Henrich, K.-O., Westermann, F. (2008) CAMTA1. In: Encyclopedia of Cancer, Second Edition. Springer. Ed. M. Schwab
[6] Westermann, F. (2008) SCF^{skp2} ubiquitin ligase. Encyclopedia of Cancer, Second Edition, Springer, Ed. M. Schwab

Personnel

Post-Doctoral Research Associates

Savelyeva, Larissa, PhD	(since 20.08.1992)
Westermann, Frank, Dr.med.	(since 01.01.2000)
Henrich, Kai-Oliver, Dr.rer.nat.	(01.08.2004-31.12.2009)
Sagulenko, Vitaliya, Dr.rer.nat.	(01.09.2007-31.12.2009)

Secretary

Kirchner, Cornelia, Secretary	(since 01.01.2001)

Doctoral students (all PhD candidates)

Afanasyeva, Elena	(01.07.2005-31.08.2008)
Blumrich, Anne	(01.04.2008-31.03.2011)
Brückner, Lena	(01.08.2008-31.07.2011
Dreidax, Daniel	(01.05.2007-30.04.2010)
Ghazaryan, Seda	(01.09.2005-31.08.2008)
Gogolin, Sina	(01.06.2007-31.05.2010)
Hormozian, Fabiola	(01.06.2005-30.09.2008)
Ibragimova, Diana	(01.05.2008-31.03.2011)
Muth, Daniel	(01.04.2005-31.12.2008)
Pöhler, Christina	(01.03.2008-28.02.2011)
Zahedi Hamedani, Sarah	(01.10.2007-30.11.2009)

Technicians

Park, Young-Gyu (Lab-Manager)	(since 01.08.2000)
Bannert, Steffen (Deputy Lab-Manager)	(01.01.2005-31.05.2011)

Teaching and Education

Lecture “Tumor Genetics” (Schwab, Westermann, Savelyeva, Henrich), Heidelberg and Kaiserslautern
Lecture PhD Programm at the DKFZ „Progress in Cancer Research“, Topic: Molecular Biology of Neuroblastoma (Westermann)

Doctoral Theses (completed):	7
Diploma	3

Third-party funding

01.10.2003-01.01.2007	Deutsche Krebshilfe (Westermann) "Molecular Characterization of Neuroblastoma after Screening" € 450.000
01.09.2004-31.05.2008	BMBF Neuroblastoma Research Network NGFN-2 "Molecular Pathways of Spontaneous Neuroblastoma Regression" (Westermann/Schwab) € 650.000
01.01.2007-01.01.2010	European Embryonal Tumor (EET) Pipeline, EU WP3 Custom ET-specific oligonucleotide-array (Westermann) WP7 Target validation: Cell Cycle (Myc and pRb) (Westermann/Schwab) € 550.000
01.06.2008-31.05.2013	BMBF ENGINE Consortium NGFN^{Plus} WP 13 Targeting MYC functions (Westermann) € 650.000
01.06.2008-31.05.2013	BMBF ENGINE Consortium NGFN^{Plus} WP 10 Fragilome Project (Savelyeva) € 650.000
01.04.2008-31.03.2011	Helmholtz-Russia Cooperation Project Bilateral Breast Cancer (Savelyeva/Schwab) € 450.000
01.06.2008-31.05.2013	Israel-MOS/DKFZ Cooperation Project Fragile Sites and Cancer (Savelyeva/Schwab) € 150.000

Patents and Licensing

Becker, Deubzer, Ehemann, Westermann, Witt O. *Helminthosporium carbonum* toxin, a specific inhibitor of histone deacetylases, reactivates impaired retinoblastoma (RB) tumor suppressor function in neuroblastoma P-731/EZ/FK

Monoclonal N-Myc Antibody (B8.4.B) against N-terminal recombinant human N-MYC to Santa Cruz, Biotechnology Inc.

Collaborations

DKFZ

Dr. T. Beissbarth, Molecular Genome Analysis, - *Analysis of ChIP-chip data*.
Dr. A. Benner, Biostatistics, - *Biostatistics*
Dr. B. Brors, Prof. Dr. R. Eils, Theoretical Bioinformatics, - *Diagnostic NB chip*.
Prof. Dr. T. Höfer, Modelling of Biological Systems, - *MYCN/c-MYC functions*
Dr. A. Hotz-Wagenblatt, Dr. K.-H. Glatting, Molecular Biophysics, - *miRNAs in NBs*
Dr. R. König, Theoretical Bioinformatics, - *Oncogenic MYCN/c-MYC signatures.*
Dr. U. Korf, Molecular Genome Analysis, - *Reverse protein arrays*
Dr. D. Mertens, Molecular Genetics, - *Expression of CAMTA1 in primary NBs.*
PD Dr. J. Mollenhauer, Molecular Genome Analysis, - *CAMTA1 mutation analysis.*

Dr. S. Pfister, Molecular Genetics, - *Expression analysis of medulloblastomas*
Prof. Dr. O. Witt, Kooperation Unit Pediatric Oncology, - *HDAC inhibitors.*

External

1. Systems Biology of Embryonal Tumors: Neuroblastoma as a Model
   BMBF Genomics Network Program NGFN-2
   National Neuroblastoma Research Network 2005-2008
   Coordinators: Schwab/Eggert

2. E.E.T.-Pipeline
   European **E**mbryonal **T**umor Pipeline
   6th European Framework Programme
   LIFESCIENCE HEALTH-6
   Coordinator: Eggert

3. ENGINE
   Extended **N**euroblastoma **G**enome **I**nteraction **NE**twork (ENGINE):
   Further Steps Towards Personalized Medicine
   BMBF Functional Genome Research for Human Health NGFN^{Plus}
   National Neuroblastoma Network, 2008-2013
   Coordinators: Eggert/Schwab

4. Diagnostic NB Chip: Molecular Characterization of Neuroblastoma
   Tumor Genetics-Children's Clinic, University of Cologne (Westermann/Fischer)

Other external partners
J. Khan, Oncogenomics Section, Pediatric Oncology Branch, National Cancer Institute, National Institutes of Health, USA

K. Ushijima, Carcinogenesis Division, National Cancer Center Research Institute, Tokyo, Japan

A. Nakagawara, Division of Biochemistry, Cancer Center Research Institute, Chiba, Japan

P. Gillespie and N. Fotouhi, Discovery Chemistry, Hoffman La-Roche Inc., Nutley, New Jersey, USA

Evgeny Suspitsin and Evgeny Imyanitov, Petrov Institute for Cancer Research, St.Petersburg, Russia

Manfred Schwab, Dr.rer.nat,

University Professor of Genetics

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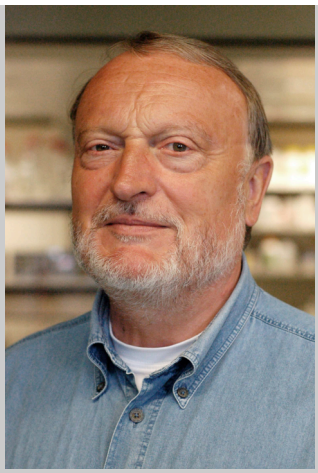

Curriculum vitae

1972	Diploma Biology, University of Giessen, Germany
1974	Dr.rer.nat., University of Giessen, Germany
1980	Habilitation (Genetics), University of Giessen, Germany
1980-1984	Visiting Scientist, University of California, San Francisco, USA
1984-1987	Assistant Professor, University of California, San Francisco, USA
1987-1992	Group Leader, Young Investigator, DKFZ (First Young Investigator at DKFZ)
1992-	Head Division “Tumor Genetics”

Research fields

- Biology and Genetics of Neuroblastoma
- FRAGILOME Project

Main personal achievements:

- Work out genetics of risk for cancer (melanoma, neuroblastoma) in a fish genetic model (Schwab (1987) Trends in Genetics 3, 38-42; Schwab (1986) Advances in Cancer Research 47, 63-97)
- First establishment and use of parallel (array) analysis for mRNA expression profiling (Schwab et al. (1983) Nature 303, 497-501)
- Discover the *MYCN*-gene and its amplification in neuroblastomas by mRNA expression profiling (Schwab et al. (1983) Nature 305:245-248), work out *MYCN*-transforming functions (Schwab et al. (1985) Nature 316, 160-162) and localisation of amplified *MYCN* to previously enigmatic abnormal chromosomal structures specific to tumor cells (Schwab et al. (1984) Nature 308, 288-291); amplified *MYCN* was the very first oncogenetic biomarker, now in clinical use worldwide for therapy design of neuroblastoma (Schwab et al. (2003) Lancet Oncology 4:472-480).

Activities in the scientific community (selected)

Editor-in-Chief: “Cancer Encyclopedia“ (Springer)

Editor-in-Chief: International Journal “Cancer Letters”

Associate Editor: Cancer Research, Oncogene, British Journal of Cancer

1994-1995 Chairman Section Tumor Genetics, German Cancer Society

1995-1996 Vice-President, German Cancer Society

1995-1996 Member, General Motors Award Panel

1998-1999 Member Pezkoller Award Panel

2003-2006 Member, Executive Committee, European Association for Cancer Research (EACR)

2000-2007 Member Managing Board, European Science Foundation COST Action B19

1996-2007 European Commission, many Assignments in Evaluating and Monitoring Panels

1985-2008 Assignments in numerous evaluation panels of grant organisations among Europe (Germany, Italy-AIRC, Cancer Research UK, Finland, Portugal, INSERM-France, and others)

2008- Member, International Steering Board, Advances in Neuroblastoma Research

2007- Chairman for Europe and Russia Region, International Board on Advances in Neuroblastoma Research

2008- Member, International Scientific Advisory Board, Regina Elena Cancer Institute, Rome

2005-2008 Coordinator (together with A. Eggert) of funded Research Network "Systems Biology of Embryonal Tumors: Neuroblastoma as a Model" within National Genome Research Network (NGFN-2), funded by Federal Ministry of Research and Technology

2008-2013 Coordinator (with A. Eggert) of funded Research Network "ENGINE **E**xtended **N**euroblastoma **G**enome **I**nteraction **NE**twork (ENGINE): Further Steps Towards Personalized Medicine", within NGFN-plus.

Honors & awards

1979 Heisenberg Award, Deutsche Forschungsgemeinschaft

1992 Deutscher Krebspreis (National Cancer Award)

1998 Gerhard Domagk Award

Publications (2003-2008)

[1] Matzner, I., Savelyeva, L. and Schwab, M. (2003) Preferential integration of a transfected marker gene into spontaneously expressed fragile sites of a breast cancer cell line. Cancer Letters 189, 207-219.

[2] Wiedemeyer, R., Westermann, F., Wittke, I., Nowock, J. and Schwab, M. (2003) Ataxin-2 promotes apoptosis of human neuroblastoma cells. Oncogene 22, 401-411.

[3] Praml, C., Saveleva, L. and Schwab, M. (2003) *Aflatoxin B_1 Aldehyde Reductase (AFAR)* genes cluster at 1p35-1p36.1 in a region frequently altered in human tumour cells. Oncogene 22, 4765-4773.

[4] Schwab, M. and Evans, A. (2003) Neuroblastoma – developmental and molecular biology meet therapy design. Cancer Letters 197, 1.

[5] Schwab, M., Westermann, F., Hero, B. and Berthold, F. (2003) Neuroblastoma: biology and molecular and chromosomal pathology. Lancet Oncology 4, 472-480.

[6] Wittke, I., Wiedemeyer, R., Pillmann, A., Savelyeva, L., Westermann, F. and Schwab, M. (2003) Neuroblastoma-derived sulfhydryl oxidase/quiescin6 family, regulates sensitization to Interferon gamma-induced cell death in human neuroblastoma cell. Cancer Research 63, 7742-52.

[7] Mädge, B., Geisen, C., Möröy, T. and Schwab, M. (2003) Yaf2 inhibits Myc biological function, Cancer Letters 193, 171-176.

[8] Sugihara, E., Kanai, M., Matsui, A., Onodera, M., Schwab, M. and Miwa, M. (2004) Enhanced expression of *MYCN* leads to centrosome hyperamplification after DNA damage in neuroblastoma cells. Oncogene 23, 1005-1009.

[9] Schwab, M. (2004) *MYCN* in neuronal tumours. Cancer Letters 204, 179-187.

[10] Kim, M.-K., Zitzmann, S., Westerman, F., Arnold, K., Brouwers, S., Schwab. M. and Savelyeva, L. (2004) Increased rates of spontaneous sister chromatid exchange in lymphocytes of *BRCA2*$^{+/-}$ carriers of familial breast cancer clusters. Cancer Letters 210, 85-94.

[11] Chen, Q-R., Bilke S., Wei J.S., Whiteford C., Cenacchi N., Krasnoselsky A., Greer B., Son C-G., Westermann F., Berthold F., Schwab M., Catchpoole D. and Khan, J. (2004) cDNA array-CGH profiling identifies genomic alterations specific to stage and MYCN-amplification in neuroblastoma. BMC Genomics 5, 70.

[12] Wei, J.S., Greer, B.T., Westermann, F., Steinberg, S., Son, C.-G., Chen, Q.-R., Whiteford, C.C., Bilke, S., Krasnoselsky, A.L., Cenacchi, N., Catchpoole, C., Berthold, F., Schwab, M. and Khan, J. (2004) Prediction of clinical outcome using gene expression profiling and artificial neural networks for patients with neuroblastoma. Cancer Research 64, 6883-6891.

[13] Büttel, I. and Schwab, M. (2004) Common fragile sites and cancer: Targeted cloning by insertional mutagenesis. Ann. N.Y. Acad. Sci. 1028, 14-27.

[14] Bilke, S., Chen, Q-R., Westermann, F., Schwab, M., Catchpoole, D. and Khan, J. (2005) Inferring a tumor progression model for neuroblastoma from genomic data. Journal of Clinical Oncology 23, 1-9.

[15] Askoxylakis, V., Zitzmann, S., Mier, W., Graham, K., Krämer, S., von Wegner, F., Fink, R.H.A., Schwab, M., Eisenhut, M. and Haberkorn, U. (2005) Preclinical evaluation of the breast cancer cell-binding peptide, p160. Clin. Cancer Res. 11, 6705-6712.

[16] Henrich, K.-O., Fischer, M., Mertens, D., Benner, A., Wiedemeyer, R., Brors, B., Oberthuer, A., Berhold, F., Wei, J., Khan, J., Schwab, M. and Westermann, F. (2006) Reduced Expression of *CAMTA1* correlates with adverse outcome in neuroblastoma patients. Clin. Cancer Res. 12, 131-138.

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[18] Savelyeva, L., Sagulenko, E., Schmitt, J.G. and Schwab, M. (2006) Low-frequency common fragile sites: Link to neuropsychiatric disorders? Cancer Letters 232, 58-69.

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[20] Suspitsin, E.N., Sokolenko, A.P., Togo, A.V., Lazareva, Y.R. Turkevich, E.A., Matsko, D.E., Henrich, K.-O., Borresen-Dale, A.-L., Schwab, M. Cornelisse, C.J. and Imyanitov, E.N. (2006) Nonrandom distribution of oncogene amplifications in bilateral breast carcinomas: possible role of host factors and survival bias. Int. J. Cancer 120, 297-302.

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(2006) Customized Oligonucleotide Microarray Gene Expression–Based Classification of Neuroblastoma Patients Outperforms Current Clinical Risk Stratification. Journal of Clinical Oncology 24, 5070-5078.

[22] Askoxylakis, V., Mier, W., Zitzmann, S., Ehemann, V., Zhang, J., Krämer, S., Beck, C., Schwab, M., Eisenhut, M. and Haberkorn, U. (2006) Characterization and development of a peptide (p160) with affinity for neuroblastoma cells. J. Nucl. Med. 47, 981-988.

[23] Chen, Q.-R. , Bilke, S., Wei, J.S., Greer, B.T., Steinberg, S.M., Westermann, F., Schwab, M. and Kahn, J. (2006) Increased WSB1 copy Number Correlates with its Over-expression which Associates with Increased Survival in Neuroblastoma. Genes, Chromosomes and Cancer 45, 856-862.

[24] Fechter, A., Büttel, I., Kühnel, E., Savelyeva, L. and Schwab, M. (2007) Common fragile site FRA11G and rare fragile site FRA11B at 11q23.3 encompass distinct genomic regions. Genes, Chromosomes and Cancer 46, 98-106.

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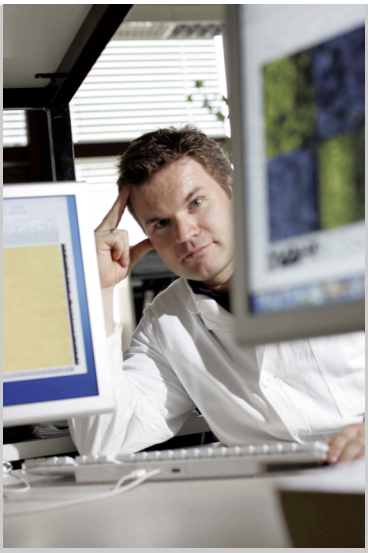

Curriculum vitae

1988-1995 Study of Medicine, University of Köln, Germany
1995 Medical State Examination
1997 Medical Liscensure (Full Approbation)
1994-1998 MD Thesis, Department of Immunogenetics, Clinic of Internal Medicine at the University of Köln (Prof. Dr. H. Tesch, Prof. Dr. V. Diehl)
”Interleukin 10 inhibits cytokine production in human AML cells”
Summa cum laude
1996-1999 Internships, Clinic of Pediatrics, University of Köln
Pediatrics and Pediatric Endocrinology
Pediatric Intensive Care Medicine
Pediatric Oncology and Hematology
2000-2001 Research Fellowship (Deutsche Forschungsgemeinschaft, DFG)
National Cancer Institute (NCI), Oncogenomics Section, Pediatric Oncology Branch, Gaithersburg, MD, USA (Dr. J. Khan)
German Cancer Research Center (DKFZ), Department of Tumor Genetics, B030, (Prof. Dr. M. Schwab)
2002- Senior Scientist and Group Leader Neuroblastoma Research in the Department of Tumor Genetics, B030, German Cancer Research Center (DKFZ)

Research fields

Functional Oncogenomics
Molecular Biology of Neuroblastoma
MYCN and c-MYC functions in tumorigenesis

Activities in the scientific community

Elected Member of the Advances in Neuroblastoma Research Advisory Board
Member of the Molecular Diagnosis and Response Prediction (NCT) Advisory Board
Consultant of the Reference Laboratory for the Clinical German Neuroblastoma Trial 2004

Honors & awards

2000 DFG Research Fellowship

Publications (2003-2008)

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1988 PhD in Biology, Institut of Cytology, Academy of Sciences, Leningrad, USSR
1988-1991 Post-Doctoral researcher, Institut of Cytology, Academy of Sciences, Leningrad, USSR, Department of Cell Morphology
1991- Post-Doctoral and senior researcher, Department of Tumorgenetics, DKFZ

Research fields

Genetic instability in cancer, *FRAGILOME* project

Publications (2003-2008)

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Curriculum vitae

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1999-2001 Research assistant, Department of Microbiology and Molecular Genetics, University of Texas- Houston Medical School, Houston, USA

2001-2005 PhD student, Department of Tumorgenetics, DKFZ

2007 Dr.rer.nat. in Biology, University of Kaiserslautern

2007- Post-Doctoral Researcher, Department of Tumor Genetics, DKFZ

Research fields

Drug resistance and novel drug targets in neuroblastoma

Publications (2003-2008)

[1] Sagulenko, E., Savelyeva, L., Ehemann, V., Sagulenko, V., Hofmann, W., Arnold, K., Claas, A., Scherneck, S. and Schwab, M. (2007) Suppression of polyploidy by the BRCA2 protein. Cancer Letters 257, 65-72.

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Curriculum vitae

1993-1999	Student of Biology at Justus-Liebig University Giessen and Glasgow University
2000-2004	PhD student, Deutsches Krebsforschungszentrum DKFZ, Dept. Tumor Genetics
2004	PhD in Genetics, University Kaiserslautern
2004-	Project Leader: Neuroblastoma, chromosomal aberrations and prognostic biomarkers

Research fields

Oncogenomics and functional oncogenomics of neuroblastoma with a focus on 1p aberrations, genomic biomarkers for the clinic, neuronal differentiation

Publications (2003-2008)

[1] Henrich, K.-O., Sander, A.C., Wolters, V. and Dauber, J. (2003) Isolation and characterization of microsatellite loci in the ant *Myrmica scabrinodis*. Mol. Ecol. Notes 3, 304-306.

[2] Henrich, K.-O., Fischer, M., Mertens, D., Benner, A., Wiedemeyer, R., Brors, B., Oberthuer, A., Berthold, F., Wei, J.S., Khan, J., Schwab, M. and Westermann, F. (2006) Reduced expression of *CAMTA1* correlates with adverse outcome in neuroblastoma patients. Clin. Cancer Res. 12, 131-138.

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