


Functional Profiling

Resources	Applications	Projects
<ul style="list-style-type: none"> Whole-genome RNAi RNAi Global / Dharmacon 12k human ORFs International ORFeome Collaboration 	<ul style="list-style-type: none"> Protein localization Functional screens <ul style="list-style-type: none"> RNAi - P38 signaling, cell detachment Overexpression - apoptosis <p>with Sven Diederichs (B150) <input type="checkbox"/></p>	<ul style="list-style-type: none"> >Expansion of resources ORF, shRNA, miRNA >Protein dynamics (subcellular localization & cellular phenotypes) >Assay development NFκB translocation, miRNA in signaling & cancer >Identification of signaling network candidates
	<p>Data analysis Candidate validation (<i>in vitro</i>, <i>in vivo</i>, clinics) Systems biology</p>	

poster U. Tschulena

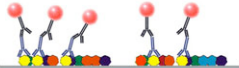
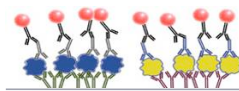
Stefan Wiemann

Molecular Genome Analysis (B050)

dkfz.

19

Quantitative Proteomics

Technologies	Specifications	Projects
<p>Reverse phase microarrays</p>  <p>Proteomics 2007</p>	<ul style="list-style-type: none"> cost-effective tumor protein profiling: (1,000 tumor samples/slide) > 80 RPPA validated ABs (different suppliers) 	<p>Tumor profiling J Pathol 2008a, J Pathol 2008b >GIST, colon, breast, prostate cancer, neuroblastoma</p>
<p>Microspot Immunoassay</p>  <p>Adv Biochem Eng Biotechnol 2008</p>	<ul style="list-style-type: none"> dose-dependent and dynamic effects of signal transduction (5% SD) sensitivity: pg/mL dynamic range: >10³ 	<p>Signaling networks PNAS 2007, Proteomics 2008 >Quantitative protein profiling >RNAi based strategies, Receptor Tyrosine Kinase inhibition</p> <p>Systems biology Proteomics in press >Quantitative analysis of ERBB and ESR1 signaling in breast cancer cell lines >Validation of network models in clinical samples</p>

poster U. Korf

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20

Integrative Cell Biology

Signaling and Cell Cycle Regulation	Cell – ECM Interactions	Cell – Cell Interactions
<p>Computational simulations and experimental validations to elucidate therapeutic strategies</p> <p>PNAS 2007</p>	<p>siRNA screen for detachment → glycosaminoglycan degradation pathway</p> <p>BMC Bioinformatics 2008</p>	<p>Vmp1 as metastasis-relevant protein involved in the formation of cell-cell contacts</p> <p>Oncogene 2008</p>
<p>ERBB signaling network</p> <p>Mechanisms of targeted therapeutics</p>	<p>Glycosaminoglycan degradation and signaling</p> <p>Influence on Integrin, TGFβ, Met signaling</p>	<p>Vmp1 in ErbB2 signaling</p> <p>Vmp1 knockout mice</p>
<ul style="list-style-type: none"> >Validation of results using patient samples >Clinical tests for combinatorial therapies 	<ul style="list-style-type: none"> >Test systems for combinatorial treatment using therapeutic antibodies and biogenic glycans 	<ul style="list-style-type: none"> >Mouse models and tissue microarrays to test VMP1 as prognostic marker

posters Ö. Sahin, A. Hussain, D. Arlt

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21

Genetics of Autism Spectrum

Patient samples



- DNA (patients) 560
- Lymphoblastoid cell lines 190
- Complete trios (for association) 250

Projects

- Whole-genome screens (IMGSAC, AGP)
 - 2q, 7q, 11p, 15q, 16p
- Association studies (SNP/microsatellites)
 - Neuronal migration: Reelin (*RELN*)
Mol Psychiatry 2003
- Candidate gene screening (Sequencing)
 - ▶ - Ribosomal protein L10 (*RPL10*)
Mol Psychiatry 2006

Consortia/collaborations

- International Molecular Genetic Study of Autism Consortium (IMGSAC)
- Autism Genome Project (AGP)
Nat Genet 2007
- The Autism Simplex Collection (TASC)

- ▶ Functional *in vitro* modeling
RPL10 mutations L206M, H213Q in neuronal cell lines
- ▶ Animal models
RPL10 knock-in mouse

▶ poster S. Klauck

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22

Translational Oncogenomics

Technologies

Microarrays, qRT-PCR, IHC
□ with Peter Lichter (B060)

Isogenic cell lines

Cellular and animal models

Development

Clinically Oriented Research

Signatures for cancer prognosis and progression

- ▶ Prostate Europ. Urol. 2008
 - ▶ clinical study
 - ▶ splicing, miRNA
- Breast
 - ▶ *ESR1*/lymphocytes Breast Cancer Res Treat 2008
- ▶ Lung Lung Cancer 2008
 - ▶ Endobronchial microsampling
- Kidney Clin. Can. Res. 2005
 - ▶ prediction of metastases

▶ posters H. Sultmann, R. Kuner

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23

Translational Oncogenomics

Technologies

Microarrays, qRT-PCR, IHC

Isogenic cell lines

Cellular and animal models

Development

Functional Analysis

Tumor gene expression networks

Breast cancer Bioinformatics 2008
▶ Prostate cancer

Gene function analysis
Melanoma, glioblastoma
▶ Prostate cancer

Therapy targets and mouse models
▶ *Tmem45B* knock-out mouse

▶ Serum biomarker screening □ with Ralf Bischoff (B120)
▶ Signal amplification

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24

Bioinformatics and Modeling

Translational Oncogenomics
Gene expression
RNAi knockdowns

Quantitative Proteomics
Protein expression
Time-resolved data

Biological Networks

Functional Profiling
LIMS
Analysis of HCS data

Integrative Cell Biology
Cellular Models

- Statistical support in the planning of experiments
- Tools, interfaces and databases (LIMS)
- Data analysis and visualization
- Functional interpretation of data
- Prediction of gene functions and pathways
- Reconstruction of cellular pathways
- Training & courses

GOstat
Meth Enzymol 2006

LIFEdb
NAR 2006

with Roland Eils (B080)

▶ poster H. Fröhlich

Major Funding (2008-2013)

High-throughput Technologies

Molecular Mechanisms of Disease / Disease Networks

Cellular screens

Protein dynamics

Signaling networks

Prognostic signatures
FOS EGR1 MYC TFRC FOLH1

Clinical validation
prostate breast

Isogenic cell lines

Network validation
EGFR ErbB2 ErbB3 beta-Actin

IG-Prostate Cancer
H. Sültmann (▶ poster)

IG-Cellular Systems Genomics
S. Wiemann (▶ poster)

NGFN

Major Funding (2008-2013)

High-throughput Technologies

Molecular Mechanisms of Disease / Disease Networks

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IG-Prostate Cancer
H. Sültmann (▶ poster)

IG-Cellular Systems Genomics
S. Wiemann (▶ poster)

NGFN

- Signaling network analysis
→ novel components
→ prediction of phenotypes
- Clinical validation of potential drug targets
- Prospective clinical studies
- Patient stratification
→ combinatorial therapies



Tumor Genetics (B030)

1. Basic and Translational Neuroblastoma Research

- **Diagnostic NB Chip in the Clinic (Poster #1)**
- **Systems Biology of MYC Oncoproteins (#2)**
- **Spontaneous Neuroblastoma Regression: A Goldmine for New Therapeutic Concepts (#3)**
- **CAMTA1, a New Tumor Suppressor on 1p36 (#4)**
- **miRNA functions in NB biology (#5)**

2. Fragilome Project (#6-9)

Head: Prof. Dr. M. Schwab
 Group Leader: Dr. F. Westermann
 Group Leader: Dr. L. Savelyeva

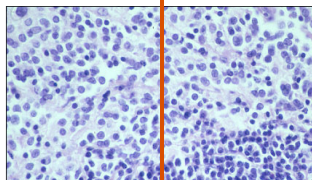


Differential Diagnostics

Clinical Courses

Unfavorable

Progression



Favorable

Regression/
Differentiation

Markers

Amplified *MYCN*

Stage

Age at Diagnosis

Error Prone

Risk Prediction/
Classifikation

High Risk

Intermediate

Low

Intensity of
Therapy

Multimodality
Treatment

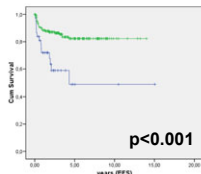


Wait-and-See

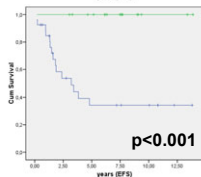
Diagnostic NB Chip in the Clinic

PAM Classifier
(144 Genes)

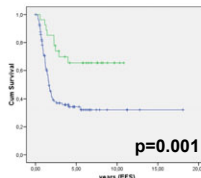
Low Risk
n = 223



Intermediate Risk
n = 43



High Risk
n = 141



- Customized NB Gene Expression Chip
 - Nature Med. 2001, Cancer Cell 2002
 - Cancer Res. 2004, Oncogene 2005
 - Clin Cancer Res. 2007

- Retrospective Study (German and International Samples, n=370)
 - JCO 2006, BMC Cancer 2007
 - Cancer Letters 2007, Clin Cancer Res. 2008

- Prospective Study since October 2004 (n=137)

- >1000 Gene Expression Profiles

- NB Chip Integrated into the German NB Trial since February 2008

- Participation in FDA-initiated MAQC2 Study (Standards for HT Data Transfer into Clinic)

Collaboration with Theoretical Bioinformatics (Brors, Eils) and German NB Study Group (Fischer)

Frank Westermann Tumor Genetics (B030)

dkfz.

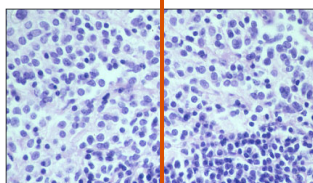
31

Progression versus Regression

Clinical Courses

Unfavorable

Progression



Favorable

Regression/
Differentiation

Genes/Pathways

?

New Therapeutic Concepts

Intensity of Therapy

Multimodality
Treatment



Observation

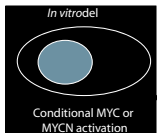
Frank Westermann Tumor Genetics (B030)

dkfz.

32

Progression versus Regression

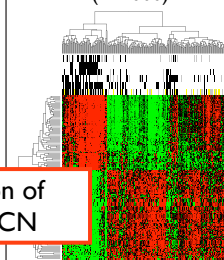
In vitro NB model systems



Functional Approaches

(cDNAs, siRNAs and Anti-Sense)
Oncogene 2003, Cancer Res 2003, Oncogene
2004, Cancer Res. 2006, Carcinogenesis 2008

Gene Expression Profiles
(n>1000)



Gene Expression Profiles +
MYCN target
Clin Cancer Res. 2007, Ca
Genome Biology in press

NB regression requires suppression of
cell self-renewal controlled by MYCN

Bioinformatics
Oncogene 2005
BMC Genomics 2005

Drug Screening

ROCHE
Patent PCT/EP2007/061206
IJC 2008, Cancer Letters 2008

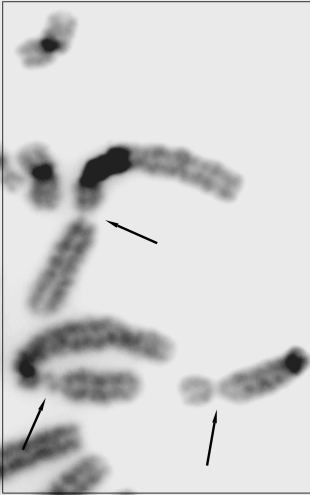
Collaboration with:
Theoretical Bioinformatics (Brors, Eils)
Molecular Genome Analysis (Beissbarth)
Cooperation Unit Pediatric Oncology (Witt)

Frank Westermann Tumor Genetics (B030)

dkfz.

33

Fragile Sites



Common Fragile Sites

- ★ are seen in **all** individuals
- ★ specific loci on metaphase chromosomes
- ★ replication stress
- ★ result in DNA breaks
- ★ molecular basis is unknown

Common Fragile Sites (CFS) and Cancer

★ Well known:

Activation of CFS can result in deletions and translocations breakpoints, oncogene amplification via breakage-fusion bridge cycles, integration of viral DNA

★ New:

Breakage at CFS is an initiating event in the generation of DNA damage at very early stages of tumorigenesis and in premalignant lesions

Aims of the FRAGILOME project

★ Identification of the full repertoire of common fragile sites in the human genome

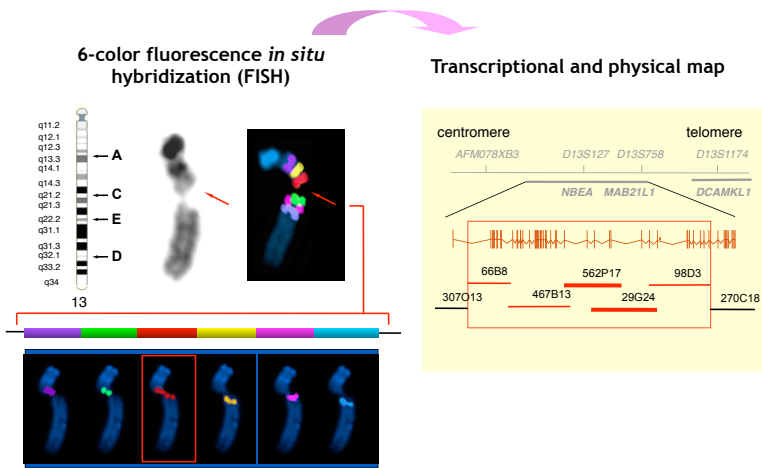
Total: ~120
Identified: 34 (20 in our department)
Unknown: ~ 90

★ Definition of significant genetic rearrangements caused by the activation of fragile sites during tumor development

Neuroblastoma
Breast cancer
Colon cancer

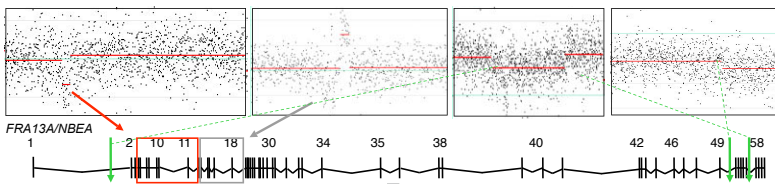
★ Development of new DNA biomarkers for diagnosis and individualized therapies

Current approach to identify CFS DNA sequences:



Genetic Rearrangements at CFS in Tumor Cells

Fine-Tiling Custom CFS Array for CGH (10bp spacing)



Preliminary data with "FRA-chip"

	1A	1C	1E	2C	2D	2E	2H	2I	2J	3A	3A'	3B	3H	9G	9C	13A	13D	14B	14C	16D	17A	
MX-1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	2
BT-20	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	9
BT-474	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	6
SK-BR-3	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	6

Breakage within CFS Genes in Breast Cancer Cells

Cooperations

Intramural

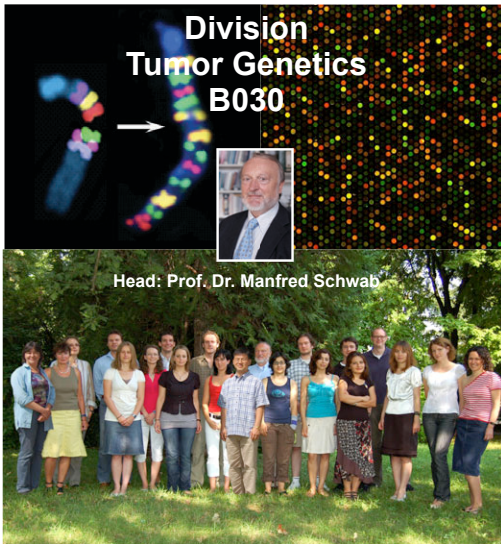
- Theoretical Bioinformatics (B. Brors, R. König, R. Eils)
- Molecular Genome Analysis (T. Beissbarth, U. Korf, S. Wiemann)
- Molecular Biophysics (A. Hotz-Wagenblatt, K.-H. Glatting)
- Modeling of Biological Systems (T. Höfer)
- Molecular Genetics (S. Pfister, P. Lichter)
- Cooperation Unit Pediatric Oncology (O. Witt)

Extramural

- M. Fischer, F. Berthold (German NB Study Group, Univ. Köln)
- A. Eggert (Univ. Essen)
- M. Eilers (Univ. Marburg)
- F. Speleman (Univ. Ghent, Belgium)
- J. Khan (NIH, NCI, USA)
- K. Ushijima (NCI, Tokyo, Japan)
- ROCHE, Nutley, New Jersey, USA (P. Gillespie)
- RNAi Screening Facility, BioQuant (H. Erfle)
- EET Pipeline Consortium (EU, 8 Partners)

Grants

- NGFN2/NGFN^{Plus} (German NB Network)
- EU EET-Pipeline
- EU MYCN/c-MYC in Embryonal Tumors
- Deutsche Krebshilfe
- DFG (Spontaneous NB Regression)
- Helmholtz-Russia Cooperation
- Intramural DKFZ Funding



Molecular Genetics of Breast Cancer (B055)

Ute Hamann

Research Activities

Determination of the contribution of the *BRCA1/2* genes to hereditary breast/ovarian cancer in non-Caucasian populations

Search for genetic factors that are associated with

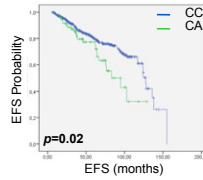
- Breast cancer risk and progression (K. Hemminki, J. L. Bermejo, DKFZ)
- Hormone therapy associated postmenopausal breast cancer risk (J. Chang-Claude, R. Eils, DKFZ)
- Hereditary breast and ovarian cancer risks

Identification of markers predictive of response to tamoxifen

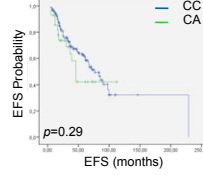
Genetic Variation of p21 and Response to Tamoxifen

- Tamoxifen can induce cell cycle arrest and apoptosis
 - A critical mediator of its effect is the cyclin dependent-kinase (Cdk) inhibitor p21
 - Nuclear p21 binds to cyclin-Cdk complexes to inhibit cell cycle progression
 - In contrast, cytoplasmic p21 can promote cell cycle progression and correlates with poor response to tamoxifen
- ↓
- p21 genetic variation may influence protein function and tamoxifen response

Tam-positive group (n=521)
 Median age at diagnosis (years): 65.4
 Median follow up (months): 56.4
 Event-free survival (EFS, months): 50.6



Tam-negative group (n=194)
 Median age at diagnosis (years): 62.1
 Median follow up (months): 42.2
 Event-free survival (EFS, months): 35.6



Coding SNP (C>A) in p21 resulting in a non-synonymous amino acid change

- CC carriers have a more favorable clinical outcome than CA carriers
- CC carriers may benefit from tamoxifen treatment

Research Activities

Determination of the contribution of the *BRCA1/2* genes to hereditary breast/ovarian cancer in non-Caucasian populations

Search for genetic factors that are associated with → **Poster #1**

- Breast cancer risk and progression (K. Hemminki, J. L. Bermejo, DKFZ)
- Hormone therapy associated postmenopausal breast cancer risk (J. Chang-Claude, R. Eils, DKFZ)
- Hereditary breast and ovarian cancer risks

Identification of markers predictive of response to tamoxifen

Investigation of the expression levels of estrogen receptor variants in early- (≤ 40 yrs) and late-onset (>math>\geq 60</math> yrs) breast cancer → **Poster #2**

Proteome-wide approach to identify SUMOylated proteins in breast cancer (M. Schnölzer, DKFZ) → **Poster #3**

Outlook

Risk Factors

- Identification of further low penetrance genes in Caucasians
 - Identification of low penetrance genes and modifiers of hereditary breast cancer risk in the Hispanic population
 - Identification of novel modifiers of hereditary breast cancer using a genome-wide approach (K. Hemminki)
- ↓

Prevention

Prognosis

- Identification of genetic factors that influence prognosis and survival
 - Identification of expression profiles with prognostic value for early- and late-onset breast cancer using a microarray approach (J. Hoheisel)
- ↓

Markers of clinical outcome

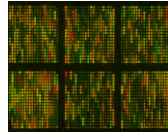
Treatment Prediction

- Identification of intrinsic and tumor-associated factors for prediction of response to tamoxifen
- ↓

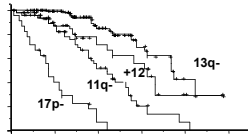
Treatment optimization targeted intervention

Division Molecular Genetics

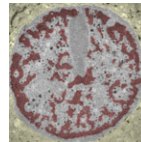
- Molecular mechanisms involved in tumor etiology and development



- Identification and validation of prognostic and predictive molecular markers

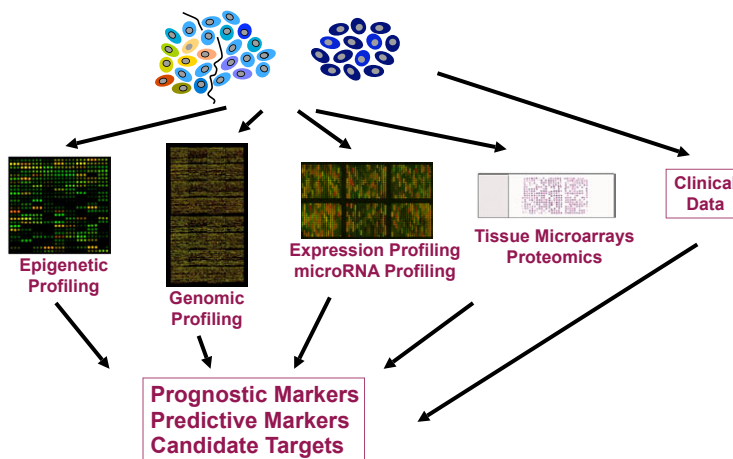


- Multidimensional structure of genomic information
Functional architecture of cell nucleus

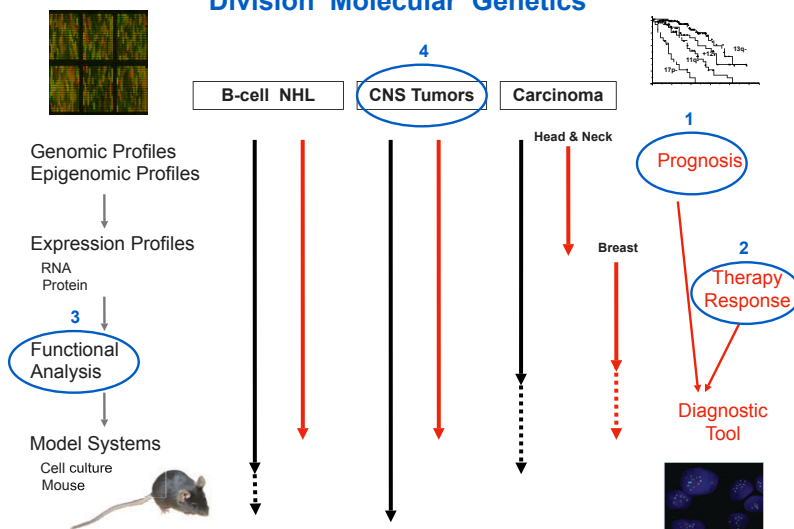


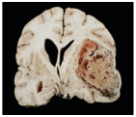
- Technology development

Integrated Analysis of Molecular Alterations



Division Molecular Genetics

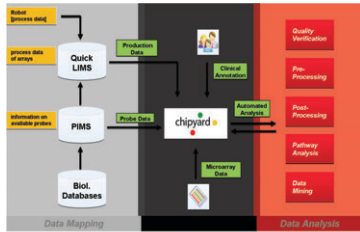




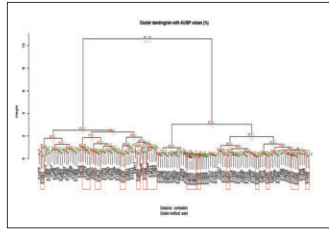
4 Glioma Core Collection (n=130)

WHO grade	II	III	IV	IV
	12	21	13	84
	Astrocytoma	Anaplastic Astrocytoma	Secondary Glioblastoma	Primary Glioblastoma

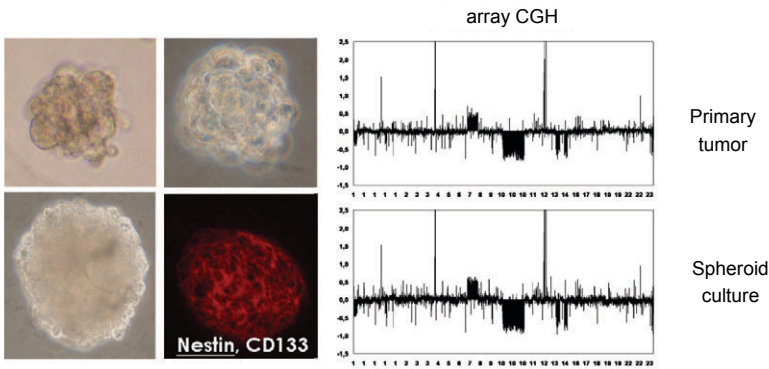
ChipYard analysis platform



Unsupervised clustering



Chromosomal Aberrations in Spheroids and Primary Tumors are very Similar

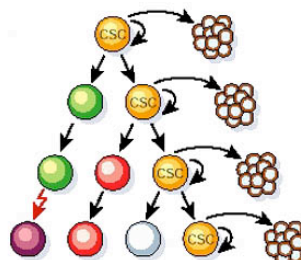


Glioblastoma neurospheres

Glioma: The Cancer Stem Cell (CSC) Concept

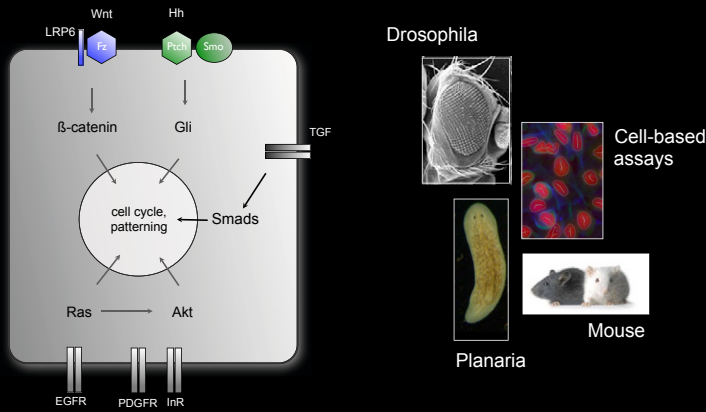
Glioma cells are heterogeneous

but: Genetic Homogeneity even between CSCs & Tumors

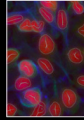


⇒ Epigenetic Regulation?
⇒ Environmental Signals?
(stem cell niche)

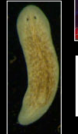
Aberrant control of conserved signaling pathways lead to developmental defects and cancer



Drosophila



Cell-based assays



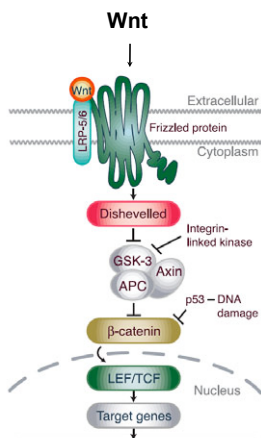
Planaria



Mouse

73

Functional analysis of signaling networks



Systematic identification of novel pathway components

Placing novel components into cellular pathways

Identification of intervention points for new therapeutic strategies

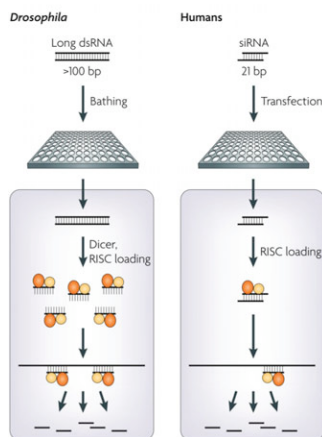
Michael Boutros

Signaling and Functional Genomics (S110)

dkfz.

74

Large-scale Functional Screens by RNAi



Boutros & Ahinger, Nat Rev Genet 2008

Michael Boutros

Signaling and Functional Genomics (S110)

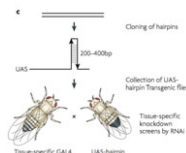
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75

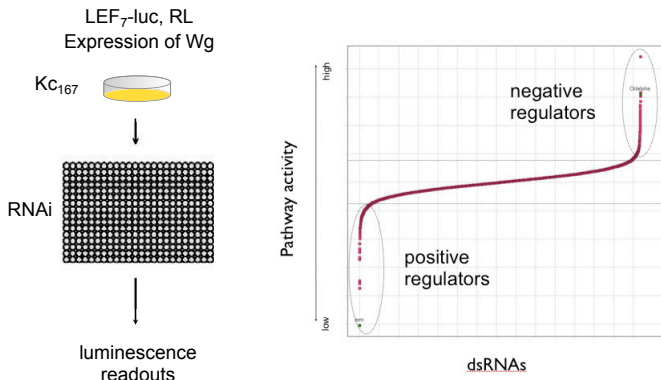
Multiple independent siRNA libraries (RNAiGlobal, S. Wiemann)

In-house design and generation of *Drosophila* RNAi libraries (FP7 CancerPathways)

Second-generation transgenic libraries with B. Dickson (IMP)



Screening for factors required for Wg/Wnt signaling in *Drosophila*



Michael Boutros

Signaling and Functional Genomics (B110)

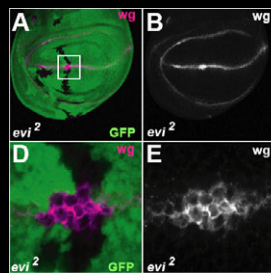
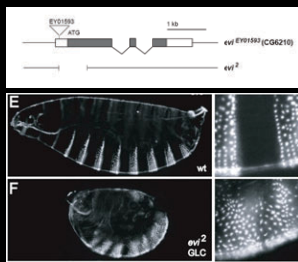
dkfz.

76

Evi/Wls is required for the secretion of Wnt growth factors

Evi has segment-polarity phenotypes identical to other core components

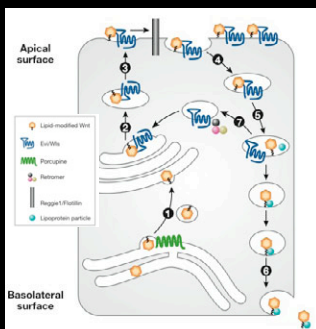
Wnt proteins are retained in the secreting cells



Bartscherer et al., *Cell* 2006

77

Wnt signaling is regulated at the level of secretion



Evi is a novel core component for Wg/Wnt signaling required for Wg secretion from *Drosophila* to human

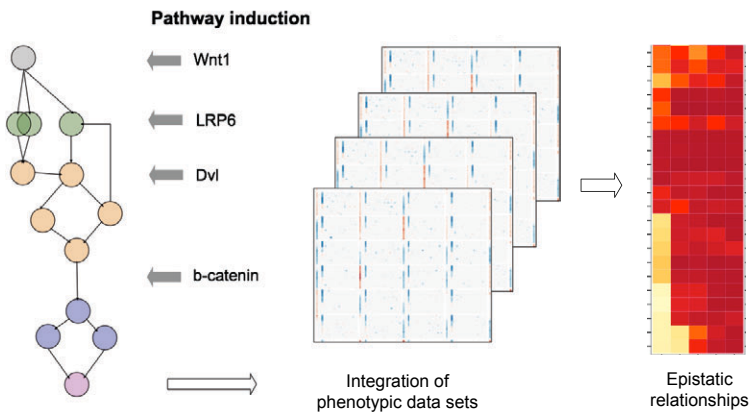
Evi requirement is specific for Wg/Wnt signaling
Required for all Wnts tested

Restricted expression, additional regulatory mechanism for Wnt

Bartscherer et al. *EMBO report* 2008

78

Reconstructing signaling networks by epistasis screens



On-going Wnt research projects

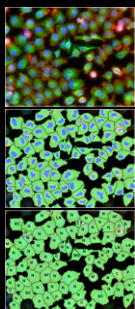
Animal models of novel signaling factors

Novel components and CRC linkage
(with K. Hemminki, Mol. Epidemiology)

Small molecule inhibitors of Wnt signaling
and interacting pathways

Building Functional Signatures of Cellular Phenotypes

Multiparametric phenotypes



multiplex reporter deep-seq

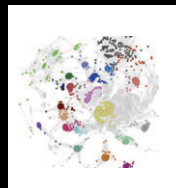
by RNAi or compounds
perturbations

computational analysis
automated

Single-cell phenoprints



Phenotype proximity to predict gene function



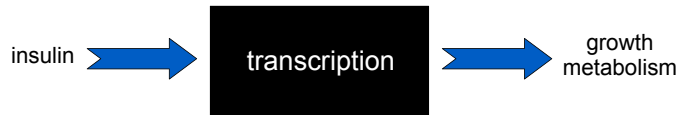
Past work

- Identified & characterized new components regulating insulin signaling

- Melted (Dev Cell 2005)
- mir-278 (Genes Dev 2006)



- Studied transcriptional output of insulin signaling



(Cell Metab 2008)

Future work / Goals

1. Insulin signaling

- how TOR activity is regulated
- new component identification via cell-based RNAi screens
- in vivo analysis of components identified in cell culture

2. Identification of components in other pathways regulating size

- Hippo
- Dpp (TGF- β)

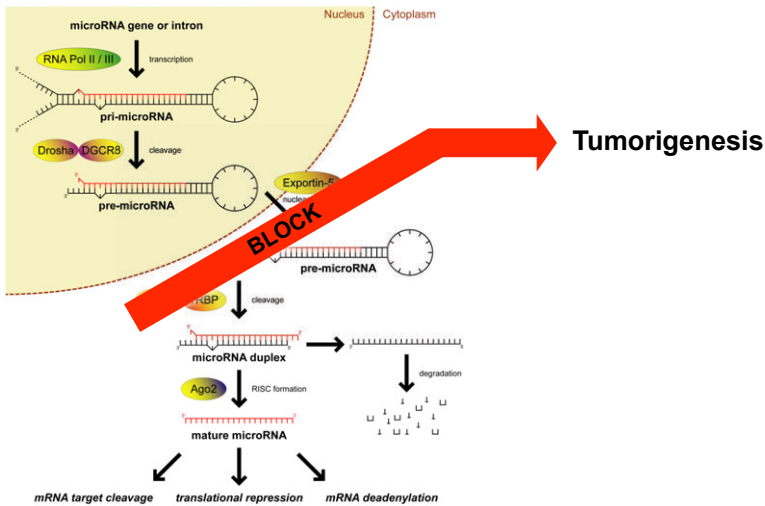
B140 Group



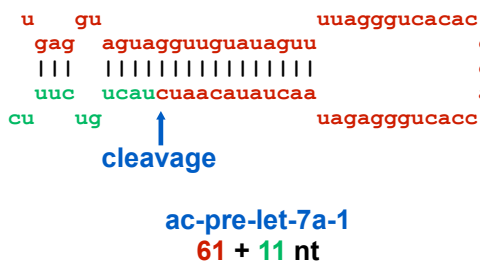
Molecular RNA Biology & Cancer (B150)

Sven Diederichs

Introduction: microRNA Biogenesis & Cancer



Previous Research: A novel step in microRNA Processing

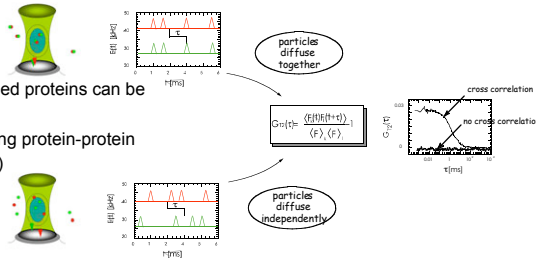


Diederichs & Haber, *Cell* 2007

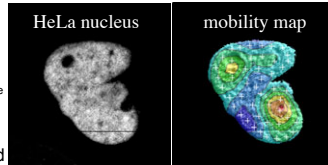
fluorescence (cross) correlation spectroscopy - FC(C)S: protein mobility and interactions in the living cell

- Dimerization of GFP/RFP-labeled proteins can be detected in vivo by FCCS: possible HT method for detecting protein-protein interactions ("two-hybrid FCCS")

(Nina Baudendistel, Waldemar Waldeck, see poster)



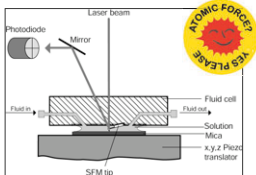
- FCS of fluorescent probes in living cells for 'mobility imaging': proteins up to 108 kDa (eGFP tetramer) can freely access the chromatin network but their mobility varies (Nicolas Dross, see poster)



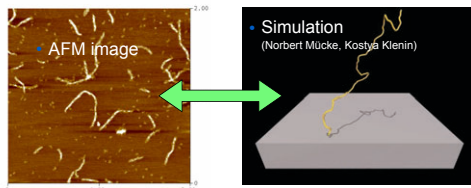
- The mobility of the actin-capping protein CapG is increased in highly invasive tumor cells (Malte Renz)

intermediate filament dynamics (Norbert Mücke, Robert Kirmse, J.L. with Harald Herrmann)

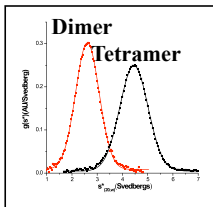
AFM - atomic force microscopy



IF proteins: vimentin, desmin, cytokeratins etc. : central role in maintaining stability of cytoskeleton



AUC - analytical ultracentrifugation



compare AFM images with computer simulations -> get structural parameters (Norbert Mücke, see poster)

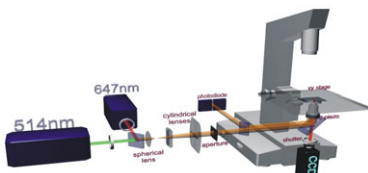
AUC, stopped-flow kinetics -> get shapes, assembly mechanism (Mücke, Kirmse, see poster)

microarray detection with single molecule sensitivity

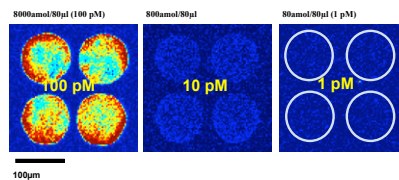
(coll. with Jens-Peter Knemeyer, Hohelsel group, and Gerhard Schütz, Uni Linz)

Detector setup

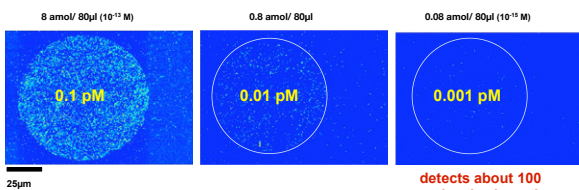
Dual wavelength laser excitation, CCD detection with single molecule resolution



Comparison (oligonucleotide sample on commercial scanner)



Same chip, single molecule detection



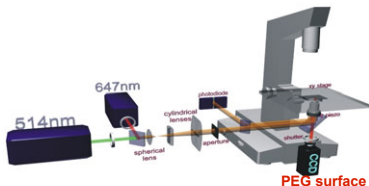
detects about 100 molecules bound

microarray detection with single molecule sensitivity

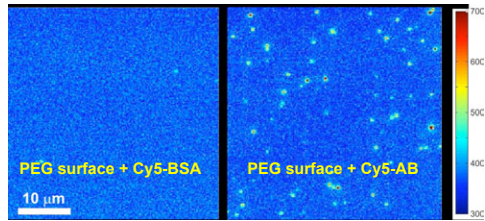
(coll. with Jens-Peter Knemeyer, Hohenseil group, and Gerhard Schütz, Uni Linz)

Detector setup

Dual wavelength laser excitation, CCD
detection with single molecule resolution

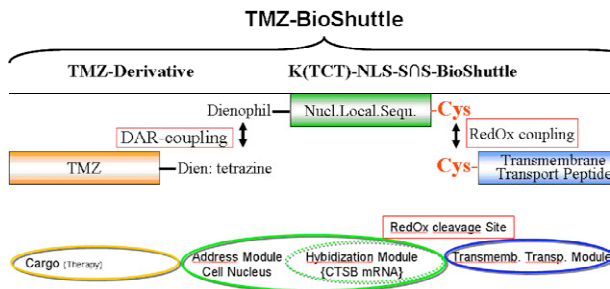


Protein detection (LAM antigen):
PEG surface from Stadler lab practically suppresses non-specific binding



BioShuttle - a cellular delivery vehicle

(Waldemar Waldeck, with Klaus Braun, see poster)



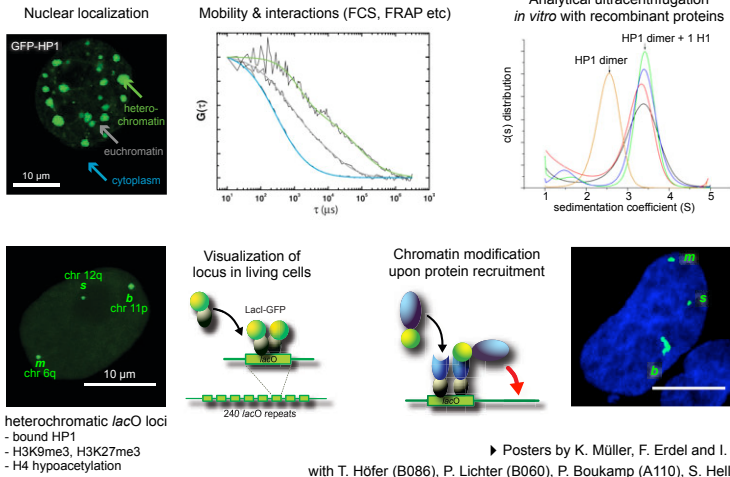
Waldeck et al. Int. J. Med. Sci. 5 (2008) 273-284

- Active cargo is connected to address module and transmembrane transport peptide
- TMZ-Bioshuttle 10 times more active on glioma cell lines than simple temozolomide
- Other cargos tested: PNAs, plasmid vectors, gadolinium (MRI)

outlook

- Single molecule fluorescence
 - short-time (ms) solution dynamics with pulsed laser excitation
 - long-time (10s) dynamics of immobilized molecules
- Single molecule observation of ligand binding to microarrays
- Rapid scanning analysis of cell arrays for measuring protein-protein interaction in vivo ('two-hybrid FCCS')
- Mobility Imaging:
 - using the mobility of fluorescent probes as an imaging parameter
- Single molecule mechanics of intermediate filaments by AFM
- 'Virtual cell nucleus':
 - Lattice model of a whole cell nucleus at nucleosome resolution

Dynamics and interactions of heterochromatin protein 1 (HP1), Suv39H1 histone methylase and linker histone H1



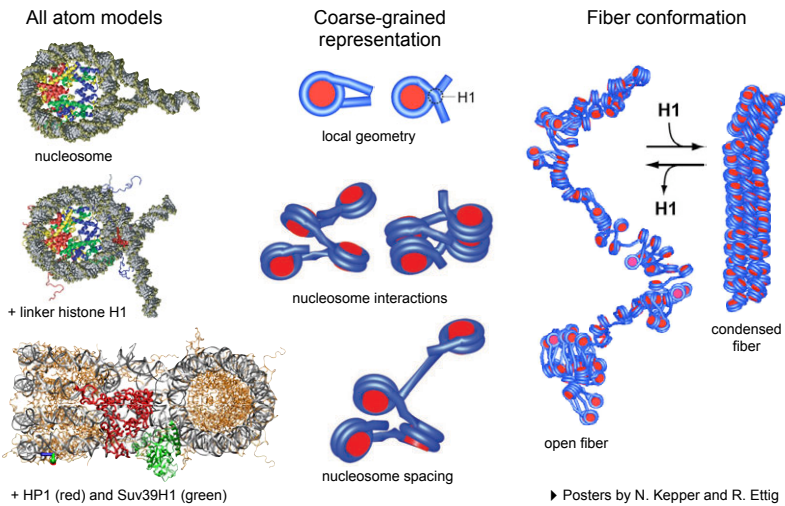
Karsten Rippe

Genome Organization & Function (B066)

dkfz.

118

A model for fiber compaction due to the binding of linker histone H1



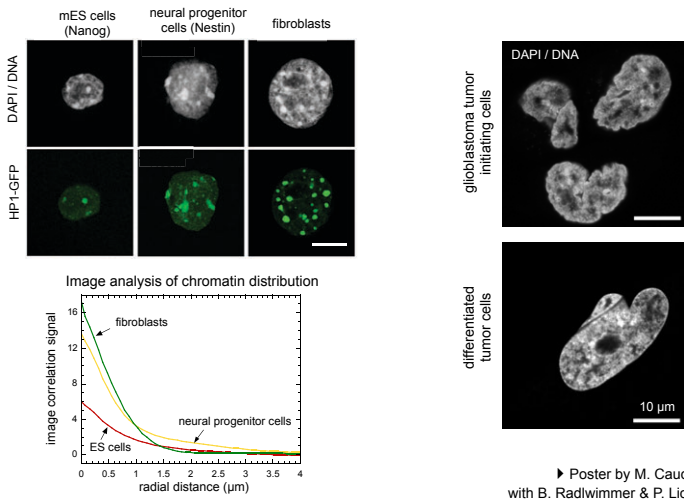
Karsten Rippe

Genome Organization & Function (B066)

dkfz.

119

Outlook: Heterochromatin formation during differentiation of mouse embryonic stem (ES) cells and tumor initiating glioblastoma cells



Karsten Rippe

Genome Organization & Function (B066)

dkfz.

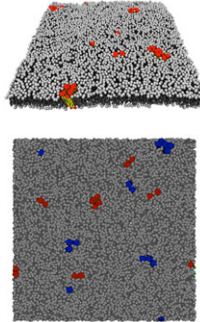
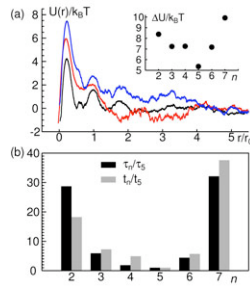
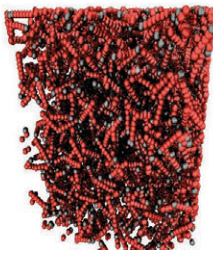
120

Beyond the diffraction limit – Mesoscopic membrane simulations

Coarse-grained molecular dynamics – faster, less information on Å-scale

Self-assembly of membranes

Oligomerization of membrane proteins due to hydrophobic mismatching



Guigas & Weiss, Biophys. J. **95**, L25 (2008)
Schmidt, Guigas & Weiss, Phys. Rev. Lett. **101**, 128104 (2008)

Matthias Weiss

Cellular Biophysics (B085)

dkfz.

136

Perspective

Quantitative (systems-) understanding of the

- regulated formation of ER exit sites and COPII vesicles
- protein sorting into COPI/II vesicles at the ER and the Golgi
- biogenesis of the Golgi apparatus
- spatiotemporal dynamics of protein and membrane traffic

Matthias Weiss

Cellular Biophysics (B085)

dkfz.

137

Protease Metabolites in Cancer (B041)

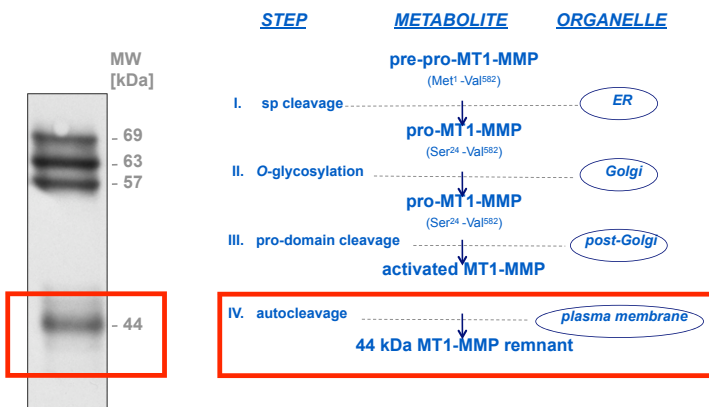
Thomas Ludwig

Membrane Type 1 Matrix-MetalloProteinase (MT1-MMP, MMP-14)

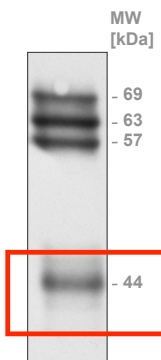
- membrane tethered transmembrane domain protease
 - spatial restriction of proteolytic activity
 - proteolytic cascade pacemaker
- potent regulator of cellular microecology
 - i.e. essential for postnatal development
 - abundant in highly invasive tumors
- protease inhibitors failed in clinical trials

REGULATION OF MT1-MMP?

METABOLIC PROCESSING OF MEMBRANE TYPE 1 MATRIX-METALLOPROTEINASE (MT1-MMP)



RATIONALE



- >90% of cell surface MT1-MMP
- lacks the catalytic domain
- N-terminally O-glycosylated
- strongly sialylated
 - conserved in all 23 human MMPs
 - catalytic activity independent effects



148



149

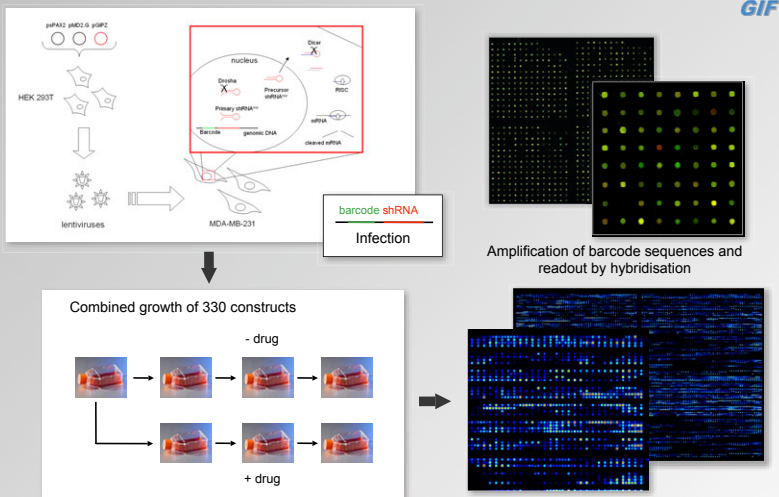
Basic Level of Functional Analysis

DNA → RNA → Protein →

Methylation	Transcription	Expression
Structure	Splicing	Localisation
Organisation	RNAi	Modification
SNPs	Structure	Combination
Copy number	Enzymatic activity	Degradation
Composition		

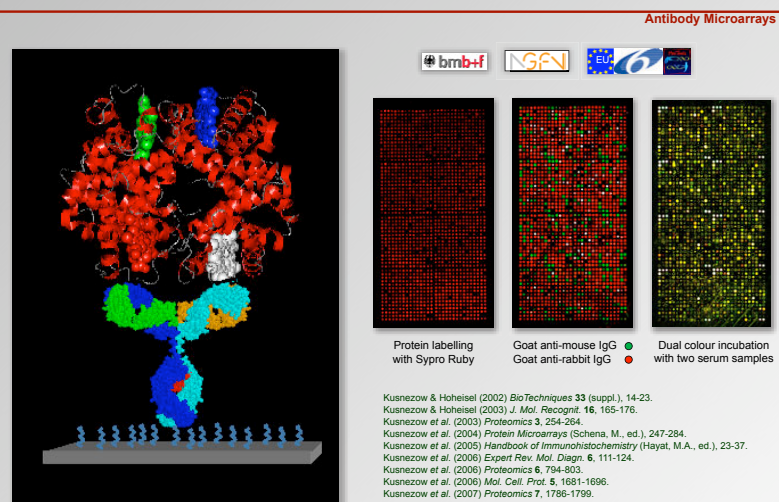
150

Simultaneous shRNA Screening



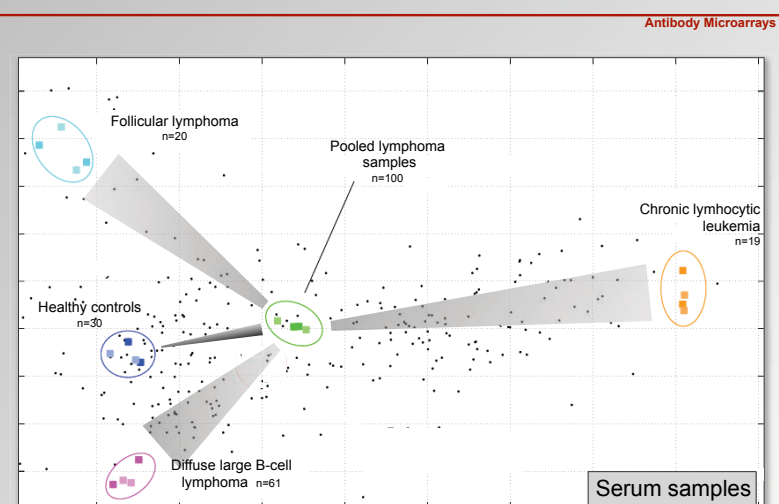
160

Complex Antigen-Antibody Interactions

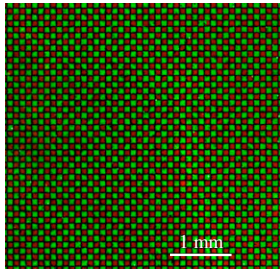


161

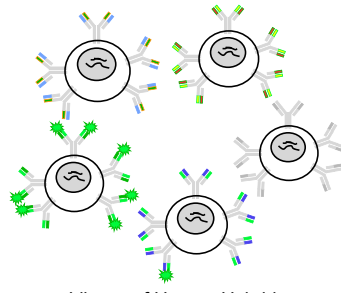
Lymphoma Study



162



High-Density Peptide Arrays

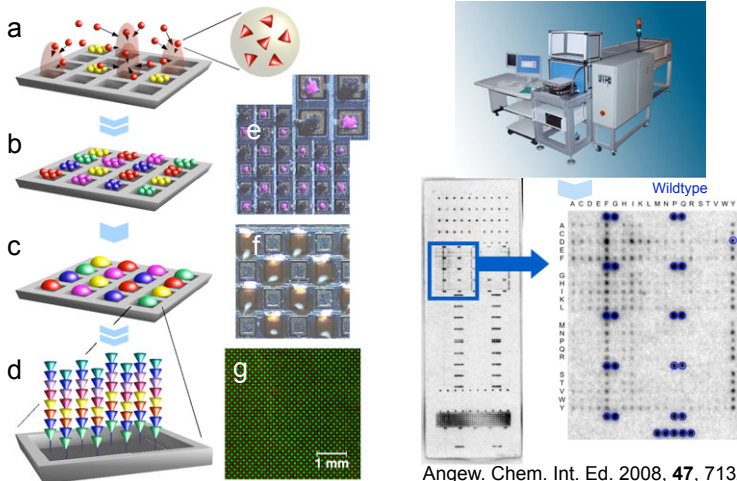


Library of Human Hybridomas

Chip-Based Peptide Libraries (B120)

Frank Breitling, Ralf Bischoff, Volker Stadler

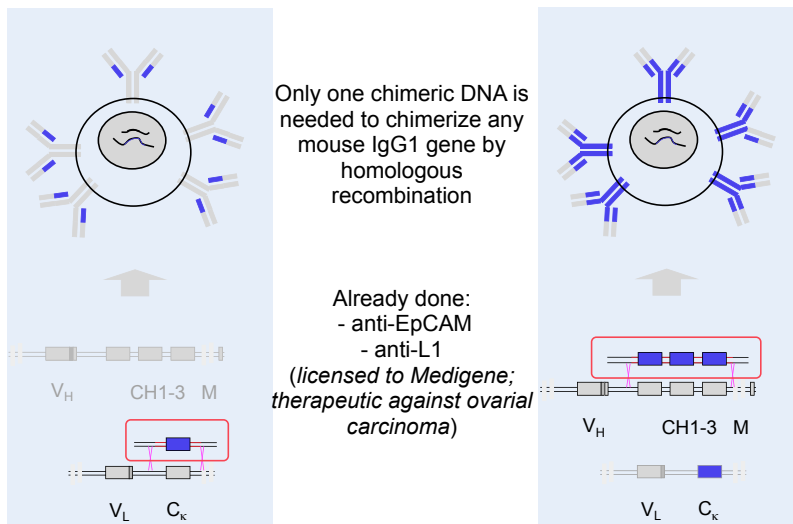
Particle-based combinatorial synthesis of peptide arrays



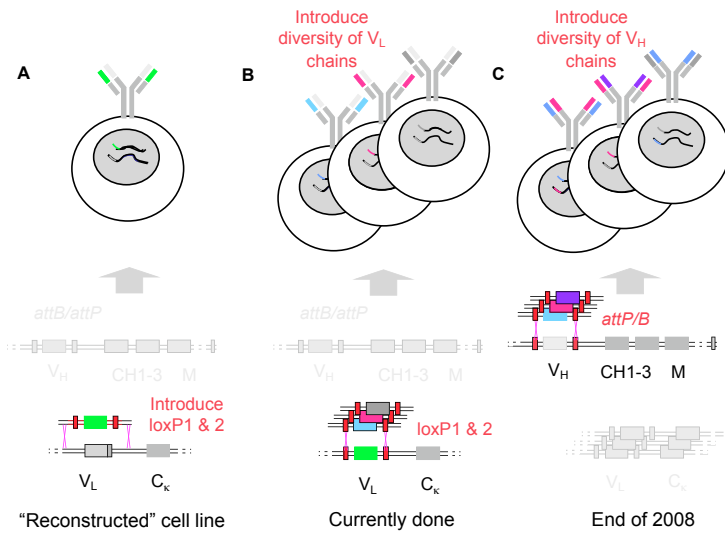
Science 2007, **318**, 1888

Angew. Chem. Int. Ed. 2008, **47**, 7132
Stifterverband Science Prize 2008

Easy method to chimerize any mouse hybridoma



Human hybridoma library by homologous & specific recombination



Frank Breitling, Ralf Bischoff & Volker Stadler

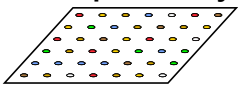
Chip-based Peptide Libraries (B120)

dkfz.

172

Applications

Peptide arrays



High affinity D-peptides as

- Therapeutics
- Antibiotics
- Scientific tools

Diagnostic peptides

- Read out antibody diversity
- MHC-presented, "T-cell arrays" (Encke, Momburg)
- Rationally designed vaccines

Targets, e.g.

- EpCAM (Moldenhauer), L1, Mesothelin (Märten), E6 (Hoppe-Seyler), Fas (Apogenix), EGFR (Alonso)

Patient's sera

(Pfreundschuh, Encke)

Human hybridoma library



Human antibodies as

- Therapeutics
- Diagnostics
- Scientific tools
- Screen for stem cell antigens

Human antibodies as

- Reverse engineered protecting antibodies

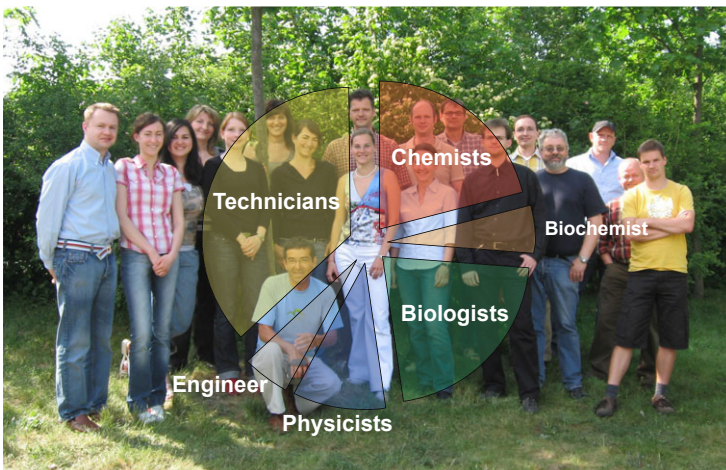
Frank Breitling, Ralf Bischoff & Volker Stadler

Chip-based Peptide Libraries (B120)

dkfz.

173

Team



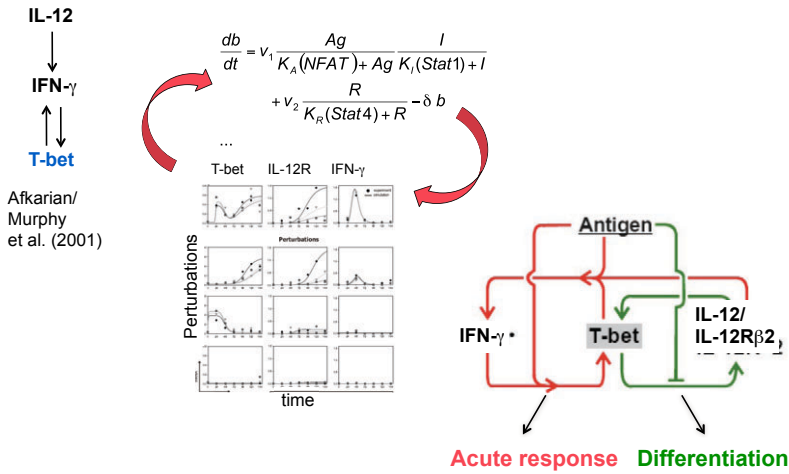
Frank Breitling, Ralf Bischoff & Volker Stadler

Chip-based Peptide Libraries (B120)

dkfz.

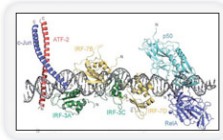
174

DYNAMICS OF T CELL DIFFERENTIATION



PERSPECTIVES

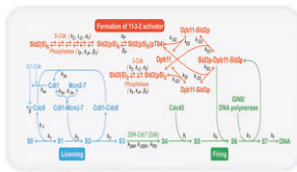
Chromatin-associated processes



DNA repair
Heterochromatin regulation

Van Driel/Vermeulen (NL)
Rippe, Grummt, Eils (DKFZ)

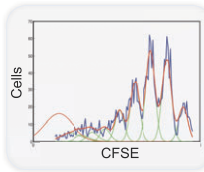
Regulatory networks



Mitogenic signaling
DNA replication

Westermann/Schwab (DKFZ)
Klingmüller (DKFZ)
Alberghina (Milan)

Cellular decisions



T-cell activation & differentiation

Radbruch/Löhning (Berlin)
Rao (Boston)
Acuto (Oxford)

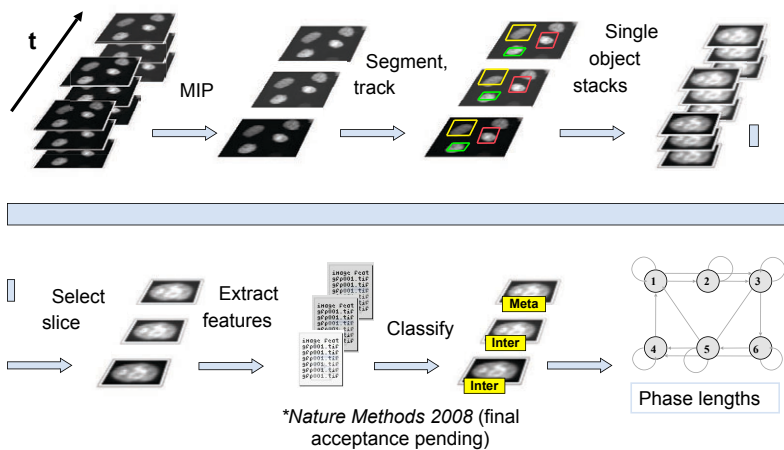


Anneke Brümmer
Carlos Salazar
Edda Schulz
Gesa von Bornstaedt
Luca Mariani
Domenico Prellino
Lu Wang
Dorothea Busse
Michael Flossdorf
Florian Lamprecht
Kristof Kally-Kullai

Funding: EU-FP7, BMBF, DFG, Helmholtz Association

Large-scale image analysis of cell arrays* (~100 mill. images)

Tracking and Classification: Cell cycle analysis. Delay assay



*Nature Methods 2008 (final acceptance pending)

Roland Eils

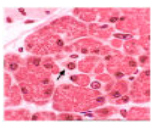
Theoretical Bioinformatics (B080)

dkfz.

184

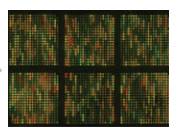
Computational Oncology

n = 10 – 1000

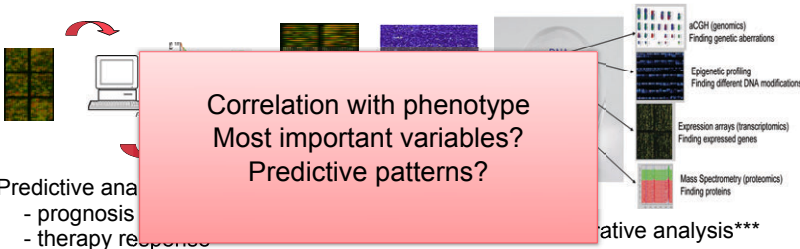


Phenotype

n = 1.000 – 30.000



Genotype



Predictive analysis
- prognosis
- therapy response

Predictive analysis***

*JCO 2006

**BMC Cancer 2007

***Clin Canc Res 2008

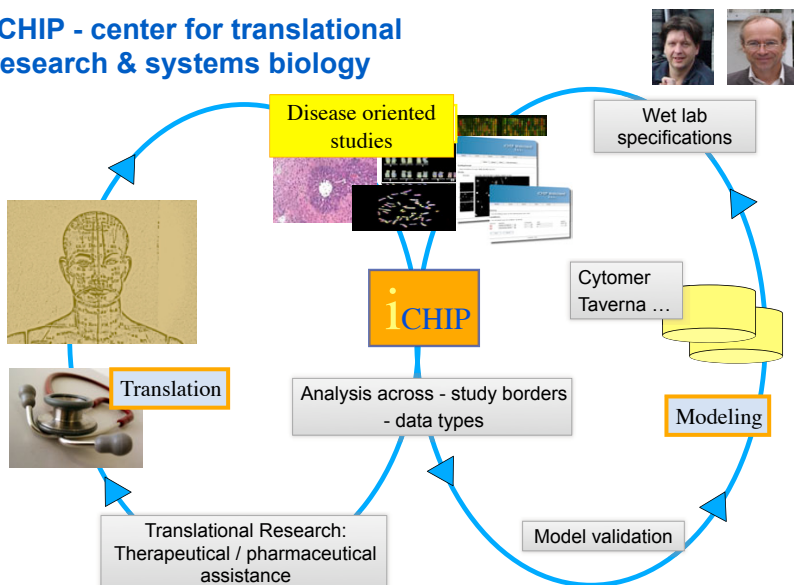
Roland Eils

Theoretical Bioinformatics (B080)

dkfz.

185

iCHIP - center for translational research & systems biology



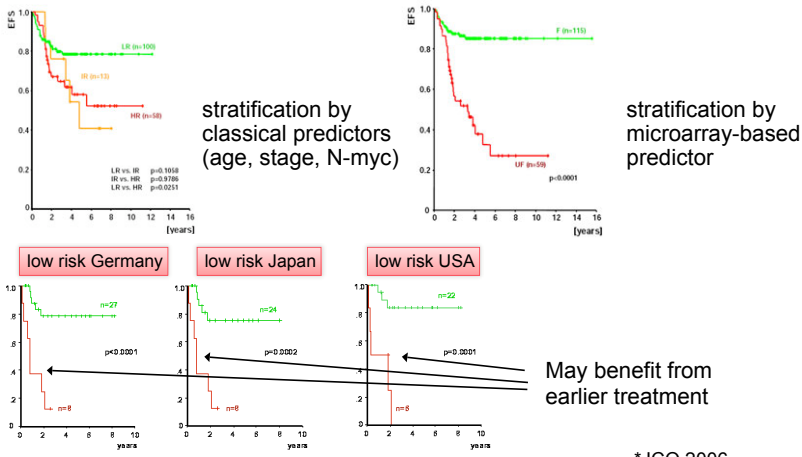
Roland Eils

Theoretical Bioinformatics (B080)

dkfz.

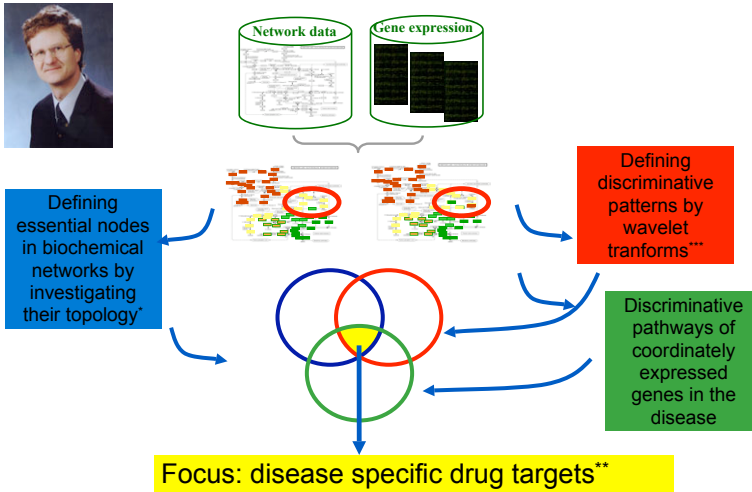
186

Improved Prediction of clinical outcome by gene expression signature in neuroblastoma*



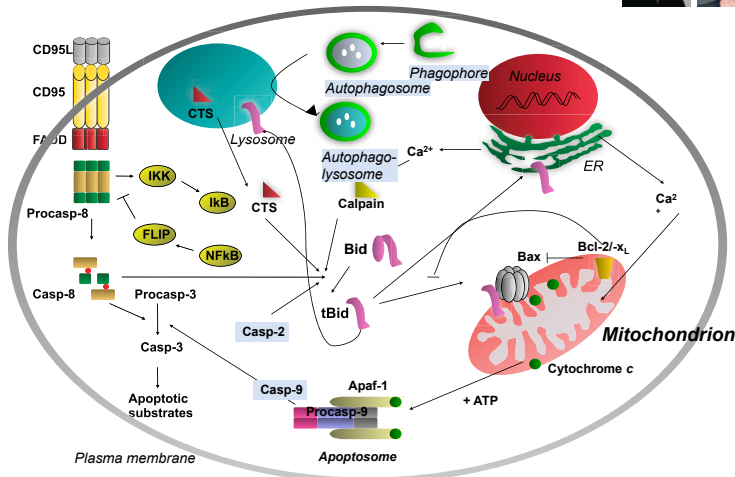
*JCO 2006

Network Modelling Group

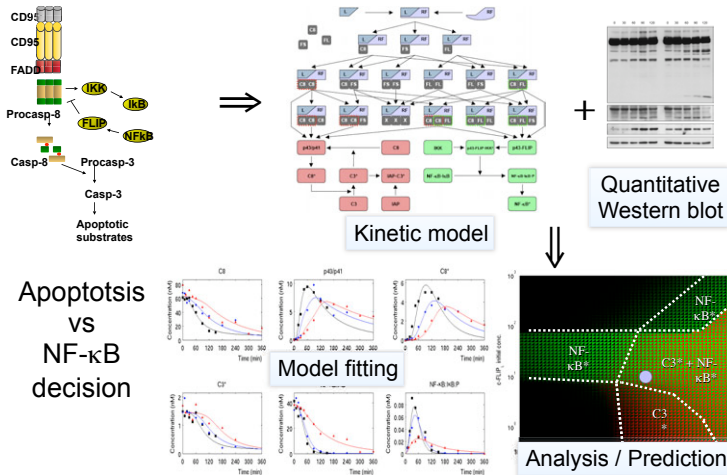


*Plaimas et al., BMC Systems Biology, 2008; ** Fatumo et al., Infection, Genetics and Evolution, 2008; ***König et al., BMC Bioinformatics, 2006

Systems Biology of Cell Death



Apoptosis regulation* and alternative pathway induction by CD95 (*JCB 2005)

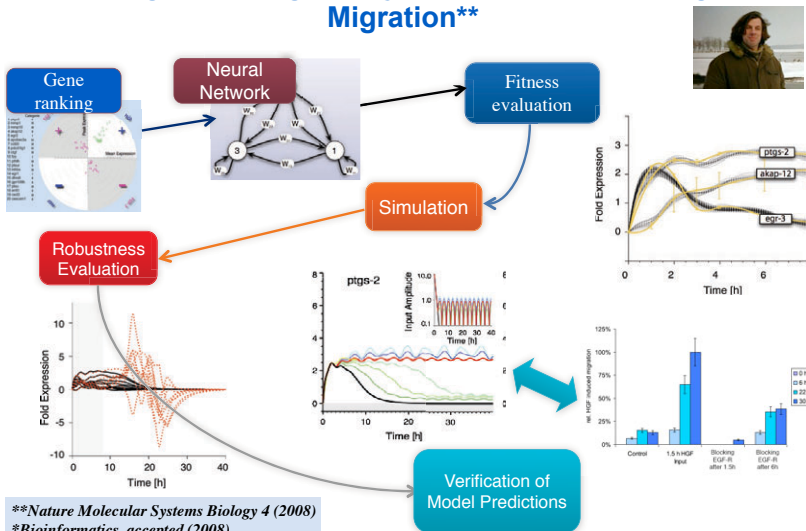


Roland Eils Theoretical Bioinformatics (B080)

dkfz.

190

Modeling Gene Regulatory Networks* Controlling Cell Migration**



**Nature Molecular Systems Biology 4 (2008)
*Bioinformatics, accepted (2008)

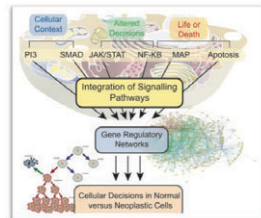
Roland Eils Theoretical Bioinformatics (B080)

dkfz.

191

Outlook

Medical Systems Biology
Systems Biology of
Complex Diseases



Synthetic Biology
From understanding to
the design of biological
systems



Roland Eils Theoretical Bioinformatics (B080)

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192

