

DKFZ-MOST Cooperation in Cancer Research

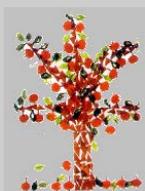
## 7<sup>th</sup> German-Israeli Cancer Research School

Hotel am Badersee, Grainau, near Garmisch-Partenkirchen

February 8 – 12, 2015

### Systems Medicine

#### Program and Book of Abstracts





## Foreword

The German Israeli Cooperation in Cancer Research, founded in 1976, has supported more than 150 joint research projects. Its 35<sup>th</sup> Anniversary was celebrated in Heidelberg on March 2013 during the 36<sup>th</sup> Meeting of the Joint Scientific Program Committee.

In 2006, during the 30<sup>th</sup> Anniversary of the Cooperation, the idea of a “German Israeli Cancer Research School” was conceived. Our aim was to bring together young scientists (students and postdocs in particular of the program) with the senior scientists in the field of cancer research from both countries, Israel and Germany, for the exchange of knowledge and ideas in a friendly and casual atmosphere.

For this 7<sup>th</sup> School of Cancer Research, the topic “Systems Medicine” was chosen. We are indebted to Profs. Galun, Rotter, Eils and Höfer for organizing the scientific program and to Nurit Topaz, Lea Loboda as well as Elfriede Mang and Corinna Sprengart for handling all administrative matters.

The 2015 meeting will be dedicated to systems medicine approaches where we will discuss different levels of regulation in the human body from a mechanistic perspective. Further, we will reconsider how these mechanisms affect people’s health. A key issue will be the role of epigenetic and transcriptional mechanisms for the development and progression of cancer and other diseases, also taking into account the impact of the environment and its effects on the predisposition for various diseases. Another focus will address the questions how aberrations in cellular decision making can lead to cancer and which roles the interaction between the tumor microenvironment and the immune system play during onset and progression of the disease.

As in the previous schools, ample time will be devoted for the informal exchange of data and ideas as well as social activities to enhance interactions amongst both the participating students and scientists.

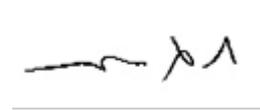
We look forward to an exciting and stimulating 7<sup>th</sup> German Israeli Cancer Research School near Garmisch-Partenkirchen.



Peter Angel  
DKFZ-Coordinator Israel-Cooperation  
and of the Schools



Varda Rotter  
Israeli Coordinator  
of the Schools



Hagit Schwimmer  
MOST Coordinator



# Program

## SUNDAY, FEBRUARY 08, 2015

Arrival in the afternoon or evening

19:30 Dinner

## MONDAY, FEBRUARY 09, 2015

### **08:30 Welcome and Introduction**

Varda Rotter, Weizmann Institute, Rehovot  
Peter Angel, DKFZ, Heidelberg

**Theme I: How Systems Medicine can contribute to Cancer Research**

**Moderator: Thomas Höfer**

### **09:00 Eytan Domany, Weizmann Institute, Rehovot**

**Pathway - Based personalized analysis of cancer**

### **09:45 Roland Eils, DKFZ, Heidelberg**

**Systems medicine for novel avenues into cancer diagnostics and therapy**

10:30 Coffee Break

### **10:45 Uwe Ohler, MDC, Berlin**

**Transcription regulation: from the identification of functional elements to predictive computational models**

### **11:30 Amos Tanay, Weizmann Institute, Rehovot**

**Epigenetic memory in development and cancer**

12:15 Skiing/winter sports

16:00 Coffee and cake

### **16:30 Poster Session**

### **17:45 General discussion: What has systems biology achieved for cancer research? What are we missing?**

**Moderator: Eithan Galun**

18:30 Dinner

19:45 Horse Sledging

## TUESDAY, FEBRUARY 10, 2015

### **Theme II: Linking Epigenetic Alterations to Disease**

#### **Moderator: Eithan Galun**

- 08:45** **Yehudit Bergmann, Hebrew University, Jerusalem**  
Epigenetic programming links intestinal inflammation to colon cancer
- 09:30** **Irina Lehmann, UFZ Leipzig, Leipzig**  
Epigenetic reprogramming by environmental factors and consequences for disease risk
- 10:15 Coffee Break
- 10:30** **Asaf Hellman, Hebrew University, Jerusalem**  
DNA methylation of transcriptional enhancers and cancer predisposition
- 11:15** **Gilad Yaakov (for Naama Barkai), Weizmann Institute, Rehovot**  
DNA damage enhances drug survival through non-mutation effects
- 12:15 Skiing/winter sports
- 16:00 Coffee and cake
- 16:30** **Poster Session by students & general discussion**

#### **Moderator: Roland Eils**

- 19:00** **Karsten Rippe, DKFZ Heidelberg**  
Integrative analysis of deregulated epigenetic networks in chronic lymphocytic leukemia
- 20:00** **“Hüttenzauber” Dinner in a traditional Bavarian mountain lodge**

## WEDNESDAY, FEBRUARY 11, 2015

### **Theme III: Modeling and Understanding the Impact of Cellular Heterogeneities**

**Moderator: Roland Eils**

- 08:45** **Thomas Höfer, DKFZ, Heidelberg**  
**Myc, tumor heterogeneity and treatment response**
- 09:30** **Nir Friedman, Weizmann Institute, Rehovot**  
**Organizing principles of dynamic T cell responses - from noisy cells to predictable populations**
- 10:15 Coffee Break
- 10:30** **Michael Hölzel, University of Bonn, Bonn**  
**Melanoma models to study the role of phenotypic plasticity and genetic heterogeneity in therapy**
- 11:15** **Eithan Galun, Hadassah Hebrew Univ., Hospital, Jerusalem**  
**The role of a microRNA and passenger strands in inflammation and cancer**
- 12:00 Skiing/winter sports
- 16:00 Coffee and cake
- 16:30** **Eytan Ruppin, The Blavatnik School of Computer Science, Tel Aviv**  
**Predicting cancer-specific vulnerability via data-driven detection of synthetic lethality**
- 17:15** **Poster Awards**
- 17:30** **Concluding Discussion**
- 19:00 Dinner



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# Abstracts of Lectures

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## **DNA damage enhances drug survival through non-mutation effects**

***Naama Barkai, Gilad Yaakov***

Weizmann Institute of Science, Rehovot, Israel

Antibiotics kill the majority of cells, yet some cells escape its toxic effects. The surviving bacteria either evolve heritable genetic resistance, or are phenotypic persisters: cells that genetically identical to their sensitive sisters, but entered a phenotypically distinct state which renders them insensitive to the antibiotics. Persistence is extensively studied in bacteria, but not in eukaryotes, although its potential significance to conditions such as fungal infection or cancer is well appreciated.

I'll describe our recent results demonstrating phenotypic persistence in the budding yeast, and our ability to isolate these cells prior to drug exposure. FACS-sorting of these cells demonstrate their ability to survive anti-fungal treatments, as well as other natural stress exposures that kill the majority of their genetically identical sister cells. I will further describe the genetic mechanism governing the transition of cells into this (transient) persistence and will discuss its possible implications for increasing genetic diversity under stressful conditions.

## **Epigenetic programming links intestinal inflammation to colon cancer**

***Yehudit Bergman***

Hebrew University, Jerusalem, Israel

Chronic inflammation represents a major risk factor for tumor formation. Epigenetic mechanisms can record the effects of environmental challenges on the genome level, and could therefore play an important role in the pathogenesis of inflammation-associated tumors. Using single-base methylation maps and transcriptome analyses of a colitis-induced mouse colon cancer model, we identified a novel epigenetic program that silences a specific set of active intestinal genes which contribute to inflammation-induced cellular transformation in mice and human.

## Pathway – Based Personalized Analysis of Cancer

*Eytan Domany*

Department of Physics of Complex Systems, Weizmann Institute of Science, Rehovot, Israel

We introduced Pathifier – an algorithm that infers pathway deregulation scores for each individual tumor sample, on the basis of expression data [1]. This score is determined, in a context-specific manner, for every particular data set and type of cancer that is being investigated. The algorithm transforms gene level information into pathway level information, generating a compact and biologically relevant representation of each sample. We demonstrated [1] the algorithm's performance on three colorectal cancer datasets, two glioblastoma multiforme datasets, and on a very extensive dataset on breast cancer [2]. We show that our multi-pathway-based representation is robust, preserves much of the original information, and allows inference of complex biologically significant knowledge, such as identifying pathways that were significantly associated with survival. We also discover new cancer sub-classes, that were not seen in direct straightforward analysis of the corresponding expression data.

[1] Pathway-based personalized analysis of cancer. Yotam Drier, Michal Sheffer, and Eytan Domany, PNAS 110, 6388 (2013)

[2] Analysis of pathway deregulation in breast cancer. Anna Livshits, M Sc thesis, Weizmann Institute, 2013, and A, Livshits et al, manuscript under review.

## **Systems medicine for novel avenues into cancer diagnostics and therapy**

***Roland Eils***

Division of Theoretical Bioinformatics (B080), German Cancer Research Center (DKFZ) and Department for Bioinformatics and Functional Genomics, Institute for Pharmacy and Molecular Biotechnology (IPMB) and BioQuant, Heidelberg University, Germany

Massively parallel sequencing (next-generation sequencing) has revolutionized research in cancer genetics and genomics and enhanced our understanding of natural human genetic variation. It has also dramatically changed the way we conduct cancer genome studies in particular in the context of the International Cancer Genome Consortium (ICGC). The German cancer genomics community has conducted massive efforts to dissect the mutational and regulatory landscape of early childhood brain tumors, in malignant lymphoma and in early onset prostate carcinoma. Despite all these efforts, the impact of cancer genome sequencing for the advancement of cancer diagnostics and therapy has been elusive. Many of our findings have remained descriptive and provided only anecdotal insights into mechanisms involved in tumor initiation and progression. While the cancer genomics community now calls for further up-scaling cancer genome sequencing from thousands to hundreds of thousands individuals it remains an open question whether generating an ever increasing amount of genomic data is sufficient to tackle the overwhelming genetic complexity of cancer. Here, I argue to complement massive cancer genome sequencing by two additional strategies. First, the massive dissection of cancer genomes needs to be accompanied by computational modeling of cancer signaling pathways to better understand the mechanistic consequences of alterations in signaling flow induced by cancer mutations. Second, we need to massively perform longitudinal genomic and epigenomic sequencing of healthy individuals from prospective population cohorts long before onset of disease to better understand the molecular basis of onset of disease. Only by tight integration of massive cancer genome data, computational modeling of information flow in cancer signaling pathways and prospective, longitudinal sequencing we will be able to impact the way we will diagnose and treat cancer in the future.

## Organizing principles of dynamic T cell responses – from noisy cells to predictable populations

***Nir Friedman***

Department of Immunology, Weizmann Institute of Science, Rehovot 76100, Israel

The adaptive immune system relies on randomness, in generating a diverse set of lymphocyte receptors through random DNA rearrangements. Randomness is also manifested in studies which show heterogeneity of lymphocyte responses, even within clonal populations of cells. This heterogeneity is believed to stem from stochastic processes, and may provide optimal performance under complex and unpredictable conditions. We investigate the interplay between randomness and order in two cases: studying the structure of the T cell receptor (TCR) repertoire, using high-throughput sequencing, and monitoring the process of CD4 T cell differentiation dynamically, using multi-color flow cytometry and live cell imaging. We show how in both cases ordered structures emerge from underlying random processes.

We find that TCR repertoire organization leads to a surprisingly large number of public sequences that are shared among individuals. These public TCR sequences are abundant, and are associated with self or modified self antigens related to autoimmunity, cancer and graft rejection.

Implications of stochasticity during CD4 T cell differentiation will also be presented, following experiments in which we mapped cell decisions dynamically at the single cell level.

## A microRNA and its spouse in p53-Mdm2 circuitry

***Eithan Galun***

The Goldyne Savad Institute of Gene and Cell Therapy, Hadassah Hebrew University Hospital, Ein Karem, Jerusalem, Israel

MiR-122 is the most abundant liver miRNA and one of the most highly expressed miRNAs in humans. miR-122 is involved in important cellular processes, including lipid metabolism, suppression of liver cancer development and Hepatitis C Virus (HCV) replication. Recently, inhibitors of miR-122 are being developed for the treatment of HCV infections. Introduction of miR-122 into tumor-derived cells was shown to reverse their tumorigenic properties establishing this miRNA as a tumor suppressor. Here we show that miR-122\*, the complementary strand of the intensively studied miR-122, possesses distinct tumor suppressor activity. We demonstrate that miR-122\* targets Mdm2, the negative regulator of the tumor suppressor p53, leading to increased cell death. Remarkably, inhibition of miR-122 by antagomiR-122 results in increased amounts of miR-122\* accompanied by decreased Mdm2 expression and elevated p53 protein levels. Our results highlight the important role that miR-122\* plays in the complex p53-Mdm2 regulatory circuit, and suggests that miR-122\* may contribute to the tumor-suppressor function attributed to miR-122.

## **Embryonic stem cell (ES)-specific enhancers specify the expression potential of ES genes in cancer**

***Asaf Hellman***

Weizmann Institute of Science, Rehovot, Israel

Cancers often display gene expression profiles resembling those of undifferentiated cells. Despite extensive research, the cause of this striking similarity remains elusive. I will describe a novel mechanism linking ES specific enhancers (ESSE) and cancer.

## MYC, tumor heterogeneity and treatment response

**Thomas Höfer**

Division of Theoretical Systems Biology, DKFZ – German Cancer Research Center, Heidelberg, Germany

While many genetic drivers of tumors are now known, their impact on cell physiology is rarely understood in terms of quantitative mechanistic models. We have studied the impact of a ubiquitous oncoprotein, MYC, by combining transcriptomics with an array of experimental techniques resolving single-cell behavior. Using the pediatric cancer neuroblastoma as a model system, we find that amplified MYCN deregulates specific cell-cycle checkpoints that control the G1-S transition in growing cancer cells and cell-cycle arrest in cells responding to chemotherapy. Iterating between mathematical modeling and experimental quantification, we identify a core checkpoint module that centers around cell-cycle regulators, retinoblastoma protein and E2F transcription factors and is functionally compromised through multiple inputs from MYCN. Thus MYCN drives primary tumor growth, apoptosis during therapy and, importantly, escape from therapy-induced senescence. Based on these insights, we find that non-genetic cell-to-cell heterogeneity and, particularly, its effects on cell-cycle progression are prime determinants of treatment response. These findings suggest combination therapy regimens to target treatment resistance.

## **A CRISPR/Cas9-based mouse melanoma model to study immunotherapies and phenotypic plasticity**

***Michael Hölzel***

Institute for Clinical Chemistry and Clinical Pharmacology, Bonn, Germany

Inhibition of oncogenic signaling, immune checkpoint blockade and T-cell therapy significantly prolong survival in metastatic melanoma patients, but relapses are the major clinical challenge. Previously, we showed that our Hgf-Cdk4 driven genetically engineered melanoma mouse model faithfully recapitulates acquired resistance to adoptive T-cell immunotherapy and we identified inflammation-induced phenotypic plasticity as key driver of relapse. As HGF is the ligand for the oncogenic receptor tyrosine kinase MET, we hypothesized that MET inhibition synergizes with adoptive T-cell transfer (ACT) therapy directed against the melanocytic antigen gp100 in our model. Selective MET inhibitors (METi) efficiently blocked cell proliferation of Hgf-Cdk4 derived murine melanoma cells (HCmel12) consistent with abrogation of MET downstream signaling in vitro. Furthermore, we observed an increased expression of the melanocytic differentiation markers tyrosinase and gp100. In vivo METi treatment inhibited the growth of transplanted HCmel12 melanomas accompanied with an enhanced pigmentation and expression of gp100. Importantly, METi did not influence the proliferation of CD8+ TCs in vitro. Therefore, we treated melanoma-bearing mice with the ACT protocol, in combination with METi or with METi alone. Mice receiving the combination showed a significantly prolonged survival suggesting that these strategies should be exploited in the clinic. Tumor heterogeneity emerges as major hurdle for targeted therapies and therefore we engineered a heterogeneous antigenic landscape using the CRISPR/Cas9 genome editing technology. Currently, we study how gp100-loss variants resist immunotherapy and explore the interplay of genetic selection and phenotypic plasticity in relapse formation. In summary, our model delineates a flexible modular approach to study the evolutionary dynamics and determinants of resistance to multimodal immunotherapies.

## **Epigenetic reprogramming by environmental exposure early in life and consequence for disease risk**

***Irina Lehmann***

Department of Environmental Immunology, Helmholtz Centre for Environmental Research – UFZ, Leipzig Germany

Epigenetic mechanisms have emerged as potential links between prenatal environmental exposure and increased disease risk later in life. We studied epigenetic changes induced by maternal environmental exposure at base pair resolution by mapping DNA methylation, histone modifications and transcription in expectant mothers and newborn children. Longitudinal whole genome bisulfite sequencing reveals that maternal exposure induces DNA methylation changes in mothers and children that were conserved over years of life. Differential methylation preferentially targets a new class of intragenic “commuter“ enhancers that show multiple, regulatory interactions with distal genes. We link the environmentally induced reprogramming of identified distal commuter enhancers to differential RNA expression and show that its epigenetic deregulation is associated with an increased risk for lung disease in children. Our results suggest that environmental exposure in the prenatal period induces a stably maintained epigenetic pattern that contributes to programming for disease later in life.

## **Transcription regulation: from the identification of functional elements to predictive computational models**

***Uwe Ohler***

MDC Berlin, Berlin, Germany

Deep sequencing technology has enabled the development of genome-wide assays that interrogate gene regulation from different angles. I will present some of our recent work to model regulatory regions, functional interactions, and the resulting gene expression by integrating these experimental with dedicated computational approaches.

## **Integrative analysis of deregulated epigenetic networks in chronic lymphocytic leukemia**

**Karsten Rippe**

Deutsches Krebsforschungszentrum (DKFZ) and BioQuant, Research Group Genome Organization & Function, Heidelberg, Germany

The cell nucleus lacks internal membrane boundaries and free diffusive transport of proteins and RNA leads to rapid mixing of soluble components on the second time scale in a size dependent manner [1]. Nevertheless, the cell adopts specific functional states during development and in response to environmental cues by establishing stable patterns of distinct chromatin states via interacting factors that set, remove and read histone modifications and DNA methylation marks [2]. In cancer cells, the disease state is frequently associated with a deregulation of the underlying epigenetic networks. To dissect this process, our current work integrates mechanistic experimental and theoretical studies of cell line model systems [3,4] with studies of primary tumor cells from patients with chronic lymphocytic leukemia (CLL). The latter is based on a comprehensive mapping of epigenetic marks that is conducted within the CancerEpiSys consortium ([www.CancerEpiSys.org](http://www.CancerEpiSys.org)). B-lymphocytes from CLL patients are compared to control cells from healthy donors to identify deregulated chromatin features with respect to histone modifications, DNA methylation and nucleosome positioning that are functionally relevant in terms of gene expression regulation. It will be discussed how epigenetic networks can control these features with a specific focus on the following issues: (i) Analysis methods that reveal linkages between different types of epigenetic marks. (ii) Rationalizing how histone modification domains adopt aberrant states via a 'nucleation and looping' mechanism [2,3]. (iii) Identification of genes relevant for the CLL disease state that display a deregulated linkage between nucleosome positioning, DNA methylation and transcription factor binding according to a mechanism proposed in our recent work [4]. Furthermore, it will be discussed how the integrative profiling of chromatin features in CLL can be exploited for pretherapeutic patient stratification.

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## **Predicting cancer-specific vulnerability via data-driven detection of synthetic lethality**

***Eytan Rupp***

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Synthetic lethality occurs when the inhibition of two genes is lethal while the inhibition of each single gene is not. It can be harnessed to selectively treat cancer by identifying inactive genes in a given cancer and targeting their Synthetic Lethal (SL)-partners. We present a data-driven computational pipeline for the genome-wide identification of candidate SL-interactions in cancer, by analyzing large volumes of cancer genomic profiles. First we show the approach successfully captures known SL-partners of tumor suppressors and oncogenes. Second, we construct a genome-wide network of SL-interactions in cancer and demonstrate its value in predicting gene essentiality. Third, we show that the co-underexpression of SL-partners has a strong positive prognostic value for cancer survival. Fourth, we identify synthetic lethality arising from gene over-activation and use it to predict drug efficacy. These results form a computational basis for harnessing synthetic lethality to uncover cancer specific susceptibilities. Indeed, we shall describe current ongoing work that builds upon this basis to predict the response of different individuals to specific drugs in a personalized based manner, using both animal models and human data.

[Joint work with Livnat Jerby Arnon, Nadja Pfetzer, Yedael Y. Waldman, Brinton Seashore-Ludlow, Adam Weinstock, Tamar Geiger, Paul A Clemons and Eyal Gottlieb]

## Epigenetic memory in development and cancer

***Amos Tanay***

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Emerging experimental approaches aim to capture transcriptional and epigenomic states at a single cell resolution. This can facilitate characterization of heterogeneous populations of single cells to define cell types and subtypes. It can also be used to study variability of gene network states and infer dynamics of regulatory differentiation and aberration that are not necessarily following a simple cell type hierarchy. Recent work from our group contributed to the development of methods for single cell RNA-seq, single cell Hi-C and deep DNA methylation. When we apply these tools to study hematopoietic development at the single cell level we uncover fuzzy and stochastic transitions between transcriptional states in populations of multipotent and progenitor cells. The current deterministic and hierarchical model for stem cell differentiation is therefore refined to include more flexible and less directional developmental programs. We will discuss what epigenetic mechanisms can underlie such flexibility and their potential impact on cancer.

## Abstracts of Posters

## miRNA High-Throughput Functional Screening Identifies Several Potential Tumour Suppressive miRNAs in Neuroblastoma

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<sup>3</sup>University of Heidelberg, Viro Quant-CellNetworks RNAi Screening Facility, Heidelberg, Germany

**Background:** Most of the functional studies of miRNAs in neuroblastoma have been based on the miRNA expression data (i.e. from RT-qPCR, array platforms or small RNA library sequencing) and have been so far aimed at single miRNA species. **Methods:** We utilized genome wide miRNA functional screening with the gain-of-function (with miRNA mimics library) and the loss-of-function (with miRNA inhibitors library) approaches in order to identify miRNAs which play a role in neuroblastoma pathogenesis.

**Results:** Phenotypic miRNA high-throughput functional screening was performed with MYCN-inducible SH-SY-5Y and the data were analysed first for putative synthetically lethal miRNAs. However, only few candidates, which fit this criterion, were retrieved. Therefore, the potential of miRNA screening was not confined to the concept of synthetic lethality, because new tumor suppressive miRNAs might be identified as well. Using these criteria, we selected 180 miRNA species from the original large scale miRNA screening. The selected miRNAs were mapped to the human genome. We retrieved five miRNAs from 1p, which showed striking growth inhibitory potential in neuroblastoma cell lines. This set included well-known mir-34a. Remarkably, the remaining four candidates have not yet been functionally characterized in neuroblastoma. Moreover, dozens of growth inhibitory and growth promoting miRNAs were mapped to two largest miRNA clusters in the human genome, C19MC at chromosome 19 and 14q32 miRNA cluster.

**Conclusion:** Our results provide an update of neuroblastoma miRNAome, with several new tumor suppressive and oncogenic miRNAs. miRNA-based therapeutics, which compensate missing tumour suppressive miRNAs or neutralizing oncogenic miRNAs identified in our screen, may be a feasible neuroblastoma therapy.

## **Metastatic potential and invasion-related forces in breast cancer cells**

***Martha B. Alvarez-Elizondo and Daphne Weihs***

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Metastasis causes nearly 90% of cancer-related deaths. Current prognostic criteria for the metastasis risk of a cancer patient provide inadequate predictors in many cases. The strongest current predictors for metastasis in various cancer types are lymph node status, histological grade, and tumor size. Those predictors are, however not infallible. A modern technique for metastatic cancer prognosis is microarray-based genetic testing that is based on differences in expression of specified genes, but requires identification of the relevant genes. Hence, for cancers with unique mutations or where prognostic markers are undetermined or unspecific, as in pancreatic cancer, such arrays are ineffective. In addition, due to the lack of standardization, clinical use of microarray technology is not yet widespread, and microarray tests are physically and financially inaccessible to most patients. Hence, new approaches are required to accurately estimate the metastatic risk. Here, we present an approach based on evaluation of the mechanical interaction of cancer cells with a soft, synthetic and impenetrable gel substrate. Using the gel system, we have successfully distinguished between highly metastatic, low metastatic potential, and non-cancerous breast cell lines. We have observed that the metastatic breast cancer cells will apply force and indent the impenetrable soft gel, while benign breast cells do not. We have also observed that cells successfully indent gels that are soft enough to indent yet stiff enough to effectively grasp. We have also observed that targeted disruption of cytoskeletal elements, such as microtubules, affect force application by the cells.

## **eIF4E and eIF4GI have distinct and differential imprints on multiple myeloma's transcriptome and signaling**

***Attar-Schneider Oshrat<sup>1,3</sup>, Drucker Liat<sup>1,3</sup>, Zismanov Victoria<sup>1,3</sup>, Tartakover Matalon Shelly<sup>1,3</sup>, Lishner M<sup>1,2,3</sup>***

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Background: the incurable plasma cell malignancy multiple myeloma (MM) is characterized with extensive protein translation. Translation is primarily regulated at the stage of mRNA recruitment to ribosomes. The predominant paradigm is that translation initiation is regulated by the coordinated function in complex of eIF4E, eIF4G and eIF4A. Yet, accumulating data indicates that eIF4E and eIF4GI (the major isoform) affect the expression of specific targets suggesting the existence of alternative mechanisms or variations on the existing model.

Aims: to assess by unbiased high throughput means whether eIF4E and eIF4GI contribute differently to MM cell's transcriptome and signaling. Thus, in RPMI 8226 eIF4E and eIF4GI knockdown models we assayed translated transcription factors, microRNAs, transcriptome and MM cells' phenotype.

Results: Significant distinction was observed between eIF4E and eIF4GI KD imprints. Major differences included: 1] TFs relevant to MM cells' tumorigenic phenotype 2] microRNAs' repertoires 3] Gene Ontology biological processes outlined a major role for eIF4E in proliferation and eIF4GI in stress responses.

Discussion: This study shows unequivocally that eIF4E and eIF4GI have distinct and separate contributions to MM gene expression and phenotype. The distinction underscores the complexity of the translational mechanism and may facilitate future therapeutics design.

## Multi-microRNA-sensitive oncolytic measles virus vectors

**Marc-Andrea Baertsch<sup>1</sup>, Mathias Felix Leber<sup>1</sup>, Sascha Bossow<sup>1</sup>, Martin Singh<sup>1</sup>, Christine E. Engeland<sup>1</sup>, Jessica Albert<sup>1</sup>, Christian Grossardt<sup>1</sup>, Dirk Jäger<sup>2</sup>, Christof von Kalle<sup>1</sup> and Guy Ungerechts<sup>1,2,#</sup>**

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We have previously established a system for post-entry targeting of measles virus (MV) by insertion of microRNA target sites (miRTS) into the MV genome, thereby repressing replication in presence of cognate microRNAs. Thus, differential expression of microRNAs, as frequently observed in normal compared to malignant tissues, can be exploited to increase vector specificity and safety.

The hypothesis of this study was that multiple miRTS for different microRNAs can be inserted into a single MV vector to detarget pivotal organs at risk without compromising oncolytic efficacy. MicroRNA-mediated attenuation of multi-tissue detargeted MV (MV<sup>mtd</sup>) was analyzed *in vitro* in Vero cells transfected with the cognate microRNAs as well as *ex vivo* in isolated primary human hepatocytes and in primary human liver slices. Oncolytic efficacy was demonstrated *in vitro* in pancreatic cancer cell lines and *in vivo* in a murine xenograft model of PC.

This work is proof-of-concept that favorable expression profiles of multiple microRNAs can be exploited concomitantly to reshape the tropism of MV without compromising oncolytic efficacy. This strategy can be adapted to different vectors and cancer entities for safe and efficient high-dose systemic administration in clinical trials.

## Role of histone mutations in brain tumors

***Pablo Bellvís, Weijun Feng, Muhammad Amir Khan, Zhe Zhu, Peng Zou, Olga Bernhardt, Hai-Kun Liu***

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Glioblastoma multiforme is one of the most common primary malignant brain tumors, with poor prognosis in both adult and children. Approximately 70%–80% of pediatric gliomas are characterized by the same mutations in the histone variant H3.3 involved in the pathogenesis of diffuse intrinsic pontine glioma (DIPG).

In this study we used an efficient brain tumor model to characterize the function and importance of the H3.3K27M mutation. RCAS vector overexpressing oncogenes and wildtype/mutant version of H3.3 were injected into P0 Nestin TVA Nestin-Cre-ER<sup>T2</sup> mice. The resulting tumor model for DIPG produces multiclonal glioblastoma and exhibit key features of the current disease. Tumor cells overexpressing H3.3K27M overgrowth other tumor cells showing the tumorigenic potential of the K27M mutation. Our model reproduces the loss of H3K27me3 observed in human DIPG carrying the K27M mutation in the H3.3. Tumors overexpressing the wildtype H3.3 show similar levels to the control tumors. Finally, glioblastomas overexpressing H3.3K27M display metastasis in the spinal cord as it has been showed to occur in around 20% of the DIPG cases.

Further on we are blocking the expression of K27M mutation using a Nestin–Cre-ERT2 mouse strain and also characterize the epigenomics of these tumors to compare it with the human DIPG.

## T cell immune responses generate diversity through linear cell-fate progression

**Michael Flossdorf<sup>1,2</sup>, Veit Buchholz<sup>3</sup>, Patricia Graef<sup>3</sup>, Dirk Busch<sup>3</sup>, Thomas Höfer<sup>1,2</sup>**

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Upon infection, naive antigen-specific cytotoxic T cells expand vigorously and give rise to a population of short-lived effector and long-lived memory cells. Conflicting models have been proposed that suggest either of these subsets to be a precursor of the other or attribute their generation to asymmetrically dividing naive cells. To gain insight into the mechanism that underlies T cell diversification we combine stochastic population modeling with large scale model discrimination based on single cell in vivo fate mapping data. Our computational framework allows for stochastic differentiation and proliferation decisions of individual cells and incorporates both symmetric and asymmetric cell division. Building on this framework, we find, first, that asymmetric cell divisions of the activated naive T cells play a negligible role and, second, that phenotypic diversity is instead generated through linear cell-fate progression: Naive cytotoxic T cells give rise to slowly proliferating, long-lived subsets from which rapidly proliferating, short-lived subsets emerge. Critical predictions of this linear differentiation model have been validated in subsequent experiments. Third, we find that recall responses initiated by resting memory T cells recapitulate the primary response.

## Epigenetic mechanism in retinoic acid sensitive and resistant neuroblastoma cells

**Moritz Gartlgruber<sup>1</sup>, Franziska Paul<sup>2</sup>, Daniel Dreidax<sup>1</sup>, Christina Schröder<sup>1</sup>, Ido Amit<sup>2</sup>, Frank Westermann<sup>1</sup>**

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**Background:** Amplified MYCN is associated with poor patient outcome in neuroblastoma. Retinoic acid (RA) is an established element of high-risk neuroblastoma therapy. RA induces neuronal differentiation in some but not all high-risk neuroblastomas. The mechanism of RA neuronal differentiation as well as resistance remains still unclear. In this study, the landscape of chromatin states and epigenetic changes upon neuronal differentiation using all-trans retinoic acid (ATRA) treatment were elucidated.

**Methods:** This was obtained by performing chromatin-immunoprecipitation sequencing (ChIP-seq). This epigenetic mechanism was compared to gene expression using RNA-seq and gene expression arrays. The neuroblastoma cell line SK-N-BE-2C served as a well-established *in vitro* model for neuronal differentiation.

**Results:** In some neuroblastoma cell lines RA treatment causes cell growth arrest and morphological differentiation. Additionally, MYCN and MYCN-bound genes are down regulated upon RA treatment. 144 h after ATRA application distinct changes in MYCN binding and epigenetic marks were observed at many different genes. Most noticeable was a shift of MYCN binding to promoter distal regions, e.g. in case of the *ALK* gene. This was associated with transcriptional down regulation of *ALK*. Moreover, there was an enrichment of H3K4me3 at the promoter region of many active genes (e.g. *NTRK1*). H3K4me3 enrichment implies transcriptional activity, which correlates with gene expression results.

**Conclusion:** Accordingly, we suggest a mechanism for gene expression regulation that is initially affected by a rapid chromatin modification in our *in vitro* model. A subsequent long term gene regulation by DNA methylation might occur later in time and has to be confirmed in further studies.

## **Pdots Nanoparticles Load Photosensitizers and Enhance Efficiently their Photodynamic Effect by FRET**

***Elina Haimov<sup>1</sup>, Hana Weitman<sup>1</sup>, Debby Ickowicz<sup>2</sup>, Zvi Malik<sup>2</sup> and Benjamin Ehrenberg<sup>1</sup>***

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A new type of nanoparticles, Pdots, and a new methodology of photosensitization are developed to achieve a more efficient photodynamic effect in aqueous solutions and in cells. Pdots are nano-sized particles, composed of conjugated chromophoric polymers coated with PEGylated phospholipids. They exhibit good aqueous colloidal properties, a broad absorption band and a strong and narrow emission band. We show that these characteristics improve biological photosensitization, which is employed in photodynamic therapy of cancer. Pdots nanoparticles load amphiphilic photosensitizers such as Rose Bengal with a high affinity, into the amphiphilic coating, without necessitating covalent attachment. At this close contact, very efficient fluorescence resonance energy transfer (FRET) occurs between the Pdot donor and the sensitizer acceptor. The Pdots serve as broad-band collectors of light, which is funneled, via FRET, to the photosensitizer. Therefore, FRET from them can additively assist to the activity of the acceptor's energy. The efficient FRET mechanism, strong uptake of the Pdot-sensitizer dyads by MCF-7 adenocarcinoma cells and their enhanced photosensitized killing are demonstrated.

## Modeling MAPK pathway alterations in pilocytic astrocytoma

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Pilocytic astrocytoma is the most frequent pediatric brain tumor, which is typically associated with MAPK pathway alterations. To characterize mutation-specific effects on cellular signaling, we developed ODE model variants describing MAPK activation in the presence of different mutations that were recently characterized in this tumor.

In case of an alteration upstream of B-Raf, as the KIAA1549-BRAF fusion or a KRAS mutation, first generation B-Raf inhibitors can induce paradoxical activation of the MAPK pathway leading to tumor growth, an effect, which is not caused by second generation B-Raf inhibitors. To simulate this paradoxical activation and to predict effects due to B-Raf and Mek inhibitor combinations, we focussed on the description of B-/C-Raf homo- and heterodimer activation and the role of the scaffold protein KSR. We implemented a recently uncovered transactivation mechanism, in which B-Raf can transactivate C-Raf but phosphorylation by active Mek is required for making C-Raf transactivation competent as well. Based on model simulations, we investigated the role of this positive feedback from Mek to C-Raf leading to a sequential activation of B-Raf homodimers and B-/C-Raf heterodimers, and the impact of variability in B-Raf and C-Raf concentrations on the proliferation behavior in a heterogeneous cell population.

Our models could reproduce experimental findings of paradoxical activation effects from first generation B-Raf inhibitors, and predict optimal combinations of B-Raf and Mek inhibitors for preventing MAPK activation in the presence of different pathway alterations.

## **Tumor stress signals contribute to tumor Resistance to Antiangiogenic Therapy**

***Adi Karsch-Bluman, Ofra Benny***

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**Introduction** Long-term anti-angiogenic therapy leads to accelerated hypoxia (low oxygen) and, consequently, tumor death due to poor diffusion of nutrients and oxygen. While tumor death is considered a desirable outcome of treatment, it also, paradoxically, contributes to tumor evasion by secreting pro-inflammatory and pro-angiogenic signals that trigger a new phase of revascularization and tumor growth.

We have demonstrated that metabolic and hypoxic tissue releases damage-associated molecular patterns (DAMPs) signals, which contribute to inflammation and angiogenesis.

**Working Hypothesis** Our hypothesis is that the suppression of blood vessels by long-term anti-angiogenic therapy triggers the release of DAMPs that act as cytokines that initiates an onset of re-vascularization that lead to “tumor resistance” to therapy.

**Objectives** Determining the angiogenic potential of fractions from hypoxic tumor cells, and identify specific proteins expressed by endothelial cells in response to exposure to these cellular fractions.

**Research Plan-** Adi Karsch-Bluman

### **Background**

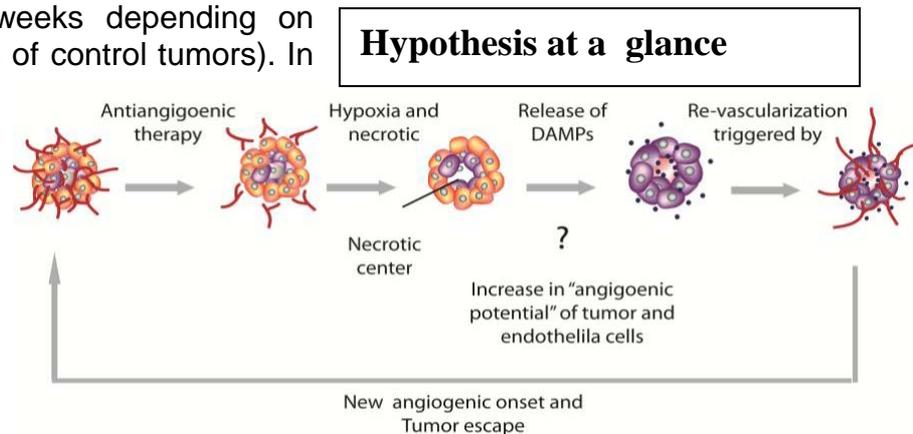
The dependency of tumor progression on the formation of new blood vessels, a multi-step process known as angiogenesis, inspired its use as a target for cancer therapy. Suppressing angiogenesis as a strategy has become an important modality for treating cancer and other vascular diseases, such as ocular diseases. However, despite the great promise of anti-angiogenic treatments, as demonstrated in numerous pre-clinical studies, the clinical efficacy of these drugs— especially as monotherapies— remains relatively limited. In practice, anti-angiogenic treatment becomes less effective at inhibiting tumor growth over time. This problem is due to tumors becoming “resistant” to these therapies but unlike resistance to chemotherapies, which is mainly caused by the unstable genetic nature of cancer cells, endothelial cells, the target of antiangiogenic drugs, are relatively stable genetically. Resistance mechanisms for anti-angiogenic drugs rely primarily on the intrinsic resistance of non-responsive endothelial cells, or, more commonly, on the upregulation of alternative compensating mechanisms, a process known as “tumor escape” or “tumor evasion”.

Long term anti-angiogenic therapy eventually leads to accelerated hypoxia (low oxygen), and consequently to tumor death due to the poor diffusion of nutrients and oxygen. By current clinical measure, this tissue death is considered a positive outcome, however, this is a double-edged sword. Several intracellular signals known as damage-associated molecular patterns (DAMPs) or alarmins are released from the dying cells due to their disrupted

membranes and act as endogenous danger signals that exacerbate inflammatory response and angiogenesis.

Our working hypothesis is that DAMPs exert direct angiogenic effects that act via a mechanism which also plays a key role in the “resistance” to anti-angiogenic drugs. According to our hypothesis, the suppression of blood vessels by long-term anti-angiogenic therapy accelerates stress (such as hypoxia), thereby triggering the release of DAMPs that act as cytokines and initiate an onset of re-vascularization, causing “tumor escape” from therapy.

Preliminary data in our lab demonstrate how anti-angiogenic therapy significantly suppresses the progression of several solid tumors. One of the broadest anti-angiogenic compounds, TNP-470, and its oral formulation that we developed, inhibited the growth of different s.c murine and human xenografts by 65-90% 2-4 weeks depending on tumor type (limited by the size of control tumors). In all of these studies after an initial response phase, treated tumors became “resistant” or less responsive to therapy in prolonged administration and eventually matched the untreated group. This trend is not drug-specific and has been found consistently in all anti-angiogenic treatments.



Interestingly, we have noticed that in anti-angiogenic treated tumors, the suppression in tumor growth was associated with accelerated death in the center of the tissue mass, frequently appeared as ulceration and open wound. Interestingly we found, in accordance with other’s published results, that the dying tissue releases signals, such as the small nuclear protein high mobility group box 1 (HMGB1) which directly affected the proliferation of endothelial cell thus contribute to angiogenesis in an inflammation-independent manner.

#### Project aims

Our goal is to study stress-induced angiogenesis in order to ultimately develop the first in its type of anti-angiogenic therapeutics with minimal drug resistance. In this proposal we aim to reveal the cellular mechanisms involved in the pathway of re-vascularization by tumor death. To achieve our goal we will pursue the following specific aims:

Specific aim 1- Develop a robust cell-based assay for stress-induced angiogenesis.

Specific aim 2- Study changes in angiogenic potential post exposure to signals secreted from the dying tumor cell.

In Aim 1 we will develop a designated cell-based assay that is suitable for screening and testing different angiogenic modulators of interest. We plan to develop a specific two-step assay comprised of tumor cells under stress by hypoxia and starvation conditions and proliferation of endothelial cells (HUVECs). This system will better mimic the unique microenvironment of the

dying tumors and will be designed for use for larger scale screenings of angiogenic mediators for future work.

In Aim 2 we plan to determine how exposure to signals released by the dying tumor cells affects the angiogenic phenotype of endothelial and tumor cells. The angiogenic potential will be determined after different levels of exposure to signals secreted of the dying cell to recapitulate the in vivo setting in which cells are located at different distance from the core of the dying cell. Endothelial and cancer cells will be analyze for their protein expression profile of more than 40 different endogenous angiogenesis mediators and a bioassay for HUVEC proliferation will be carried out to determine functionality effects.

## The mutant p53-cancer stem cells paradigm

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Our research is focused on resolving questions pertaining to genome stability in the stem and primary cells. Our experimental model takes advantage of Germline mutations in TP53 gene that were shown to be associated with cancer predisposition of patients with the Li-Fraumeni syndrome (LFS). In tumors harboring a mutation in a single p53 allele, both sporadic and LFS tumors, the majority of them undergo p53 loss of heterozygosity (LOH), which plays a main role in carcinogenesis. The goal of our research is to understand the dynamics and kinetics of the population takeover throughout the course of LOH in in vitro murine model and in tissues from human LFS patients. In our experiments we suggest to follow changes in the epigenetic genomic landscape that might affect the expression of genes involved in LOH or the LOH process by itself. Finally, we expect to identify the key genes involved in the LOH process and assess their role in the kinetics of this process.

## **Unexpected complexity of miRNA-mediated regulation of breast cancer progression by isomiRs – an example**

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During the last years, next-generation sequencing data revealed the fact that miRNA biology might be more complex than previously anticipated: in addition to the known miRNA molecules, a variety of modifications thereof have been encountered. These 'isomiRs' can differ in their 3' and 5' part, i.e. starting or ending at genomic positions different from the mature miRNA annotated in databases. Further, they can also contain non-template modifications such as 3' nucleotide additions or internal base exchanges.

Interestingly, it has been shown that 5'isomiRs which have a shifted seed sequence compared to their canonical counterpart target overlapping, but distinct sets of genes to synergistically target common pathways. However, previous studies failed to prove high-level expression of the investigated 5'isomiRs.

Here, we identified a highly expressed 5'isomiR of a previously described tumor-suppressive miRNA targeting stem cell factors in breast cancer. Using miRNA-seq data of breast cancer patients, we could link elevated expression the isomiR to improved prognosis and less aggressive tumors. This is also reflected in cellular models of breast cancer where overexpression of the isomiR but not of the canonical miRNA represses both cell proliferation and motility. Further, we identified several targets exclusive to the isomiR explaining these phenotypes.

In summary, we suggest that the canonical miRNA acting on cell differentiation together with the isomiR affecting cell proliferation and motility are synergistically exhibiting tumor-suppressive effects in breast cancer. This concept might prove effective also in cancer therapy.

## MYCN-dependent heterogeneity in cell cycle entry in neuroblastoma

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In the treatment of cancer, new interest has been sparked in the interference with the proliferation machinery to drive cancer cells into a state of apoptosis or cell cycle exit. To effectively interfere with the cell cycle machinery, an understanding of its mechanisms and its deregulation in the cancer of interest are required. In the solid childhood tumour neuroblastoma, enhanced proliferation is observed in cells with amplifications in the transcription factor MYCN, which is associated with drug relapse and poor prognosis. MYCN's promiscuous binding abilities with paradoxical effects make it difficult to understand its oncogenic potential. To elucidate the role of MYCN in cell fate, we combined time-resolved single-cell and large-scale population approaches. Transcriptome analysis of populations with differential MYCN-expression revealed that many MYCN-associated differences are cell cycle-dependent, while only a fraction of genes showed cell cycle-independent differential expression. Based on these measurements we developed a data-driven mathematical model of the cell cycle entry demonstrating that small expression differences in few key genes are sufficient to account for the MYCN-associated differences in cell cycle behaviour. The bistability of this network explains why MYCN-low cells show a large heterogeneity in their ability to enter the cell cycle and are highly sensitive to perturbations, while MYCN-high cells rapidly enter a new cell cycle, narrowing the time-window for successful interference and treatment. Using time-lapse microscopy and flow cytometry we confirmed the bimodality of the network in neuroblastoma. Thus, MYCN controls the switch between cycling and non-cycling states and facilitates the transition through the G1-phase of the cell cycle. With our data-driven model we have generated a mechanistic basis to not only study the factors governing cell cycle entry in neuroblastoma but also test the expected success of relevant treatment options.

## **A novel method for high resolution mapping of T cell receptor repertoires for characterization of public sequences associated with self- related immunity**

***Michal Mark***

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T cells recognize a huge variety of antigens, relying on their large diversity of T cell receptors (TCR) that are composed of  $\alpha$  and  $\beta$  chains. The diversity of the TCR repertoire is essential for specific immune response against a wide range of pathogens as well as for anti-tumor immunity. The composition of the TCR repertoire of an individual at a given time provides a current and past profile of the state of the immune system. Thus, measuring the repertoire can be used as a diagnostic tool for monitoring the immune response in cases such as infectious diseases, autoimmune situations and cancer.

Following the advent of high-throughput sequencing methods, significant progress has been made in the field of studying TCR repertoires (TCR-seq). Previous TCR-seq methods developed by us and others were based on a multiplex PCR approach, relying on multiple primers (e.g. ~20 primers in TCR $\beta$  of mice) for the variable region. Such methods induce biases during library preparation thus may results in less accurate data. To overcome these limitations, we developed an innovative TCR-seq method that is less prone to PCR bias, more sensitive for low-level of starting material (as low as 100 T cells) and is more cost and labor efficient. Our method is based on a nested approach for target enrichment which combines TCR $\beta$  mRNA capture beads and an internal specific RT primer. We introduce unique molecular identifiers (UMIs) for bias-free estimation of transcript abundance and used Illumina TruSeq protocol for RNA-seq to provide an anchor region in the variable side.

Recently published work from our lab revealed a set of “public” CDR3 $\beta$  sequences that are found to be shared by 28 mice and are enriched with antigenic specificities that are associated with self-antigens, including tumor-related T cells. With our novel method, we plan to further investigate these public clones, their phenotype and characterize the associated antigens. By revealing the role of public clones in immune responses, we may provide a high resolution monitoring tool for cancer and other self-associated immune conditions. In addition, as public clones are abundant and shared by many individuals, they serve as promising candidates for targeted immunotherapies.

## Early transcription dynamics during stem cell differentiation

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During embryonic development signaling pathways act repeatedly in different contexts to pattern the emerging layers. Understanding how these responses are regulated is a central question for developmental biology. In this study, we focus on early events at the interface of self-renewal and lineage specification in mouse embryonic stem cells (ESCs). Specifically, inhibition of the Erk signaling pathway is important to sustain a pluripotent ground state, and hence we ask to what extent does Erk activation shape the initial trajectory of differentiation. We employ an integrative approach, combining analysis of protein phosphorylation and gene expression changes in an inducible cellular model, together with exploration of the underlying transcription factor (TF) networks.

## Identification of Breast Cancer Subtypes Using RNA-Seq Data

***Dvir Netanel, Ron Shamir***

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Breast cancer is one of the most common types of cancer with more than 450,000 deaths each year worldwide. It is a very heterogeneous disease, making it very hard to treat effectively. Traditionally, breast cancer tumors were categorized into three therapeutic groups, each with its own clinical protocol. This classification was based on factors such as tumor size, histologic grade and hormone receptor status.

In the past decade, several studies used gene expression microarrays to develop breast cancer subtype predictors. The PAM50 predictor, which uses a molecular signature of 50 genes, can now distinguish between four intrinsic subtypes of breast cancer: luminal A, luminal B, HER2-enriched and basal-like.

In this study, we have attempted to improve the classification of breast tumors to biologically distinct subtypes by analyzing a large RNA-Seq dataset containing 961 primary breast tumor samples. Our unsupervised analysis partitioned the tumors into several clusters exhibiting partial concordance with the PAM50 classes. Whereas the basal-like and HER2-enriched subtypes were quite easily separable from the rest, the Luminal samples were not clustered in agreement with the two PAM50 Luminal subtype labels.

Interestingly, when clustering the 417 samples labeled as Luminal-A by PAM50, two major subgroups emerge, each exhibiting a distinct expression profile. Differentially expressed genes separating these two luminal-A subgroups include a large number of immune-system related genes, suggesting a key biological feature underlying the sample partitioning. Additional characteristics of the discovered Luminal-A subgroups are currently explored in order to establish whether they hold meaningful clinical importance.

## Construction of a novel target module for redirecting universal CARs against PSCA positive cells

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**BACKGROUND:** Prostate cancer (PCa) is the most common noncutaneous malignancy in men. Novel therapeutic approaches are urgently needed in hormone-refractory metastatic PCa. The prostate stem cell antigen (PSCA), is expressed in >80% of primary PCa samples and in bone metastases. Its expression level is positively correlated with advanced clinical stage and progression to androgen-independence. Therefore PSCA is a promising target for immunotherapy of advanced disease by retargeting T-cells to tumor cells.

**METHODS:** A novel anti PSCA single chain variable fragment (scFv) was constructed as a target module (TM) for redirecting of universal chimeric antigen receptor T-cells (CAR). The TM contains an E5B9 tag, which enables the binding of universal CARs, and a His-Tag at the C-terminus for purification and detection of the TM. The third tag is located between the His and the E5B9 tag and designed for labeling with radionuclides. The construct was cloned into a lentiviral vector and transduced in Chinese hamster ovary cells (CHO), which stably expressed the construct. TM was purified and protein expression and binding properties were tested.

**Results:** TM expression was proved using anti-His and anti-E5B9 antibodies via western blot. Specific binding of the TM to PSCA was confirmed by flowcytometry using PSCA positive and negative cell lines.

## Identifying regulators of the telomerase employing Mixed Integer Linear Programming approaches

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Telomeres are nucleoprotein structures protecting the eukaryotic chromosomal ends. Because they shorten with each cell division, telomere length maintenance is important for cell proliferation and survival. Telomeres can be elongated by the telomerase which is only expressed during development and in highly proliferative cells as well as in unicellular organisms like yeast. Around 80-90% of cancer cells elongate their telomeres by up-regulation of the telomerase. Hence identifying and intervening regulation of the telomerase is a promising research topic for translational oncology. To note, in 10-15% of cancer cells there is a further mechanism based on homologous recombination called alternative lengthening of telomeres (ALT).

We studied the regulation of the telomerase (*EST* genes) in *Saccharomyces cerevisiae* by using gene expression data of deletion strains and ChIP-binding data. With our mixed-integer linear programming approach we identified regulators best predicting the gene expression of the *EST* genes in yeast deletion strains with aberrant telomere length compared to strains with normal telomere length. We found interesting candidates which regulate the *EST* genes and directly bind to the telomere, as for example the subunit of the RNA polymerase II mediator complex Srb2 and the chromatin silencing-factor Sum1. All three regulators lead to telomere shortening when deleted and are not known as regulators of the *EST* genes so far. This approach is now also used to explain the regulation of telomerase (TERT and TERC) in different cancers, starting with glioblastoma.

## Characterization of the tumor-infiltrating lymphocyte (TIL) repertoire in melanoma and pancreatic cancer

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Tumor infiltrating lymphocytes (TIL) are known to confer a positive prognostic impact in most human cancers and can be harnessed therapeutically with striking clinical results in patients with metastatic cancer.

We performed next-generation T-cell receptor (TCR) gene sequencing and found enriched TCR-species in TIL as compared to matched patient blood. We hypothesize that these large T-cell clones are tumor-reactive.

Despite being present in the tumor, relevant T-cells might function poorly in vivo, due to the immunosuppressive microenvironment or „exhaustion“, as a result of repeated antigen encounter. We clearly detect such phenotypes in the majority of both melanoma and pancreatic cancer TIL, as measured by multiparametric flow cytometry of markers such as PD-1, Lag-3 and CRTAM.

We will extend these studies to monitor TCR repertoires under different conditions, such as in immunotherapy responders/non-responders, to evaluate whether they can serve as biomarkers for immunotherapy clinical trials. In parallel, there is a collaborative effort to generate similar data in well defined mouse models. These murine data will serve as the basis for mathematical models describing tumor-immune interactions, which will then be compared to experimental data from human samples and used to predict optimal strategies for therapeutic interventions.

## The lineage oncogene MITF antagonizes a proinflammatory cell state by repressing AP-1

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Malignant melanoma is a highly aggressive skin cancer. Recently we showed that inflammation elicits reversible dedifferentiation and phenotypic plasticity of melanoma cells driving resistance to immunotherapy and angiotropic metastasis in mouse models. Melanoma cell lines are highly variable in their responses to inflammatory signals like the cytokine TNF $\alpha$ , and human melanomas are likewise heterogenous with implications for disease progression and therapy resistance. The determinants of this heterogeneity are so far not known.

In an unbiased functional approach, we used gene expression data of TNF-stimulated melanoma cells together with RNAi loss-of-function and ChIP studies to identify critical determinants of proinflammatory cell states.

We show that the melanocytic master transcription factor MITF-M suppresses proinflammatory gene induction. Inversely, MITF<sup>low</sup> melanoma cells exhibit a primed TNF-responsive cell state consistent with enrichment of gene sets regulated by the NF- $\kappa$ B and AP-1 transcription factors that are both canonical components of the TNF signaling cascade. MITF directly binds to the promoter of c-Jun, a key factor of the AP-1 complex, and MITF loss results in c-Jun induction that synergizes with the TNF-alpha driven transcriptional responses. Furthermore, MITF<sup>low</sup> melanoma cells show high expression levels of c-Jun and its binding partners FOSL1/2 that explains the constitutive activity of NF- $\kappa$ B and AP-1 controlled gene programs in these cells. Importantly, MITF<sup>low</sup> primary human and murine melanomas recapitulate rewiring of this transcription factor network with increased TNF-responsive gene set activity and enhanced immune cell infiltration.

Our results identify melanoma dedifferentiation as an active feed-forward mechanism to reinforce an inflammatory cell state shaping the tumor microenvironment.

## Epigenetic silencing of MHC class I chain-related protein A and B in Merkel cell carcinoma: Improved immune recognition after reversal

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Merkel cell carcinoma (MCC) is a very aggressive, but also highly immunogenic skin cancer associated with the Merkel cell polyomavirus (MCPyV). Generally, both viral infection as well as malignant transformation induces the expression of MHC class I chain-related protein (MIC) A and B. MICs signal cellular stress to cells of the innate and adaptive immune system, such as NK and T cells, via Natural Killer group 2D (NKG2D). Consequently, MIC expression on target cells results in NKG2D mediated immune recognition and subsequent elimination of target cells.

We demonstrate here, that despite malignant transformation and the continued presence of virally-encoded proteins, MICs are only expressed in a minority of MCC tumors *in situ* and completely absent on MCC cell lines *in vitro*. This lack of MIC expression was due to epigenetic silencing via MIC promoter hypoacetylation; indeed, MIC expression was re-induced by treatment with the histone deacetylase (HDAC) inhibitor vorinostat in combination with mithramycin A *in vitro* and in a mouse xenotransplantation model *in vivo*. Most importantly, re-induction of MICs rendered MCC cells more sensitive towards immune cell mediated lysis.

In summary, we provide evidence that epigenetic silencing of MICs is an important immune escape mechanism of MCCs and that MIC re-induction by HDAC inhibitors might substantially add to the success of currently investigated immunotherapeutic approaches towards MCC.

## **Organ specific cancer incidence in an industrial subdistrict: a population-based study with 12 years follow-up**

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Although Emissions from petrochemical industries has been recognized as a cause of an increase of deaths cancer, its contribution to specific organ cancer incidence has not been investigated in a cohort study with an adequate sample size.

We assessed the association between cancer incidence and living in the Haifa subdistrict, which houses major industrial facilities in Israel. A Historical prospective study using baseline measurements from the Central Bureau of Statistics 1995 census was conducted. The hazard ratio to develop cancer comparing Haifa subdistrict to non- Haifa was 1.16 (95% CI: 1.11-1.21,  $p < 0.001$ ) after adjusted for age, gender, Jews vs. non-Jews and continent of birth. Compared to the incidence in the rest of Israel, the Haifa subdistrict population had an elevated HR of lung, head and neck, colorectal, gastric and esophagus, bladder and cervical carcinoma. In discrepancy with this observation, people in the Haifa sub-district do not smoke more than in the rest of Israel.

We report an increased risk of developing cancer in a heavily industrialized sub-district, mainly among sites which are very similar to cancer sites caused by smoking.

## Klotho a novel tumor suppressor in colon cancer

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Aberrant activation of the canonical Wnt pathway is implicated in the pathogenesis of colorectal cancer (CC). The key effector of this pathway is  $\beta$ -catenin, which functions with T-cell factor/lymphoid enhancer factor (TCF/LEF) to activate expression of target genes. Klotho is a transmembrane protein which can be shed and act as a hormone. Klotho-deficient mice manifest a syndrome resembling accelerated aging, while klotho overexpression extends life span. Klotho is a tumor suppressor in breast and pancreatic cancers and recent data indicated klotho as a potent inhibitor of the Wnt pathway. We therefore aimed at deciphering the effects of klotho on CC. Klotho overexpression inhibited colony formation of CC cells HCT 116, SW480, HT-29, Colo-320 and RKO, and daily administration of klotho to mice inhibited formation of polyps induced by azoxymethane. While klotho did not affect the IGF-1 and bFGF signaling pathways, it reduced Wnt3A and  $\beta$ -catenin protein levels and inhibited transcriptional activity of the Wnt pathway in luciferase assay. Since the effect was abrogated by transfection with constitutively active  $\beta$ -catenin, we suspected that klotho inhibited the pathway upstream of  $\beta$ -catenin. Indeed, Co-IP studies indicated direct interaction between klotho and Wnt3A.

As the inhibitory effect of klotho on colony formation was only partially rescued by transfection with constitutively active  $\beta$ -catenin, we conducted a cDNA expression microarray to explore additional mechanisms that may contribute to the effect of klotho on CC cells. The candidate genes identified suggest involvement of klotho in endoplasmic reticulum (ER) stress and the unfolded protein response (UPR).

Our data indicate klotho as a potent tumor suppressor in CC and suggest its role for it already at the stage of polyp formation. Klotho effects in CC are partially mediated by the Wnt pathway, however, additional mechanisms, possibly associated with ER stress, are involved.

## **The role of anti-apoptotic Bcl-2 proteins for colorectal cancer development and progression**

***Anna-Lena Scherr, Bruno Christian Köhler and Henning Schulze-Bergkamen***

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The Bcl (B-cell lymphoma)-2 protein family is mainly known due to its pivotal role in the regulation of the mitochondrial death pathway. Besides their inhibitory effects on mitochondrial activation, anti-apoptotic Bcl-2 proteins, such as Bcl-2, Bcl-xL and Mcl-1, also regulate cell cycle and proliferation. In colorectal cancer (CRC), which is the second most common malignant neoplasia in women and men worldwide, changes in the expression levels of anti-apoptotic Bcl-2 proteins have been described. Since especially the prognosis of patients with metastasized CRC is still very poor, we wanted to investigate whether these proteins might influence other mechanisms contributing to the malignancy of the disease like proliferation, migration and invasiveness. Migration assays in a 3D cell culture system demonstrated that siRNA mediated downregulation of Bcl-2, Bcl-xL and Mcl-1 leads to a striking impairment of migration and invasion of CRC cells.

Fortunately, this also holds true for chemical inhibition of the anti-apoptotic proteins with a pan-Bcl-2 inhibitor. This may help to identify individual treatment approaches in the near future, since strategies for inhibition of anti-apoptotic Bcl-2 proteins have already entered late-phase clinical trials.

## **The multifaceted effects of primary tumor excision on breast cancer metastasis and their inhibition by COX inhibition and a $\beta$ -adrenergic blockade**

**Lee Shaashua, Shamgar Ben-Eliyahu**

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Evidence suggests that the perioperative period for the removal of a primary tumor in cancer patients is characterized by processes that promote the outbreak of pre-existing micrometastases and the initiation of new metastases. This rather short period of time in the course of cancer progression has been shown to be pivotal in determining long-term cancer outcomes. However, cancer adjuvant therapies (commonly chemo- and radio-therapies) avoid this important time-frame, and miss an important opportunity to control or abrogate the metastatic process. The reasons for avoiding adjuvant therapies during the peri-operative period include their clinical contra-indications to tissue healing. However, other therapeutic approaches are feasible during the peri-operative period. Specifically, recent findings have pinpointed peri-operative surgical stress responses as significant pro-metastatic mediators. The excess secretion of catecholamines and prostaglandins was shown to suppress immunity, and affect both the tumor and its microenvironment to enhance cancer progression. Our laboratory have developed and assessed the effectiveness of a simultaneous blockade of catecholamines and prostaglandins during the perioperative period in several murine models. In my current work we employ a human breast cancer xenograft, injected to the mammary fat pad of Nude mice. During the perioperative period of excising this primary tumor, a short term blockade of catecholamines and prostaglandins is given to mice undergoing either an extensive or a minimal invasive surgery. Our results indicate that the extent of the surgical procedure impact metastatic burden, and that our combined drug treatment completely abolish the added effects of surgery. Employing a high-sensitive method of bioluminescent imaging, we are able to identify the initiation of the metastatic process and the effects of both surgery and the drug treatment alongside metastatic development. As several interrelated mechanisms most likely underlie these effects, our future aim is to characterize various host physiological processes and malignant tissue samples from mice at several time points along this process in order to elucidate the various mechanisms involved, and develop a multifaceted integrated model of peri-operative metastatic progression. Specific interventions and biological manipulations will assist in deducing causal relationships.

## **miR-122\*, the passenger strand of miR-122, acts as a tumor suppressor by targeting Mdm2**

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The tumor suppressor p53 is at the hub of a plethora of signaling pathways that control the cell cycle and maintain the integrity of the human genome. Mdm2 has been identified as a critical regulator of p53, which binds and inhibits many of p53's activities. The p53-Mdm2 circuitry is subjected to complex regulation by a variety of mechanisms, including miRNAs. We found a novel effector of this regulatory circuit namely, miR-122\*, the passenger strand of the abundantly expressed liver specific miR-122.

In this study we demonstrate that the levels of both, miR-122\* and miR-122, are reduced in human hepatocellular carcinoma (HCC) samples. Significantly, we found that miR-122\* targets Mdm2, thus participating as an important player in the p53-Mdm2 circuitry. In vivo tumorigenicity assays demonstrate that miR-122\* is capable of inhibiting tumor growth, emphasizing the tumor suppressor character of this miRNA. We therefore suggest that miR-122\* is an important contributor to the tumor suppression activity previously attributed solely to miR-122.

Furthermore, we show that blocking miR-122 in murine livers with an antagomiR-122 (a reagent in the process of drug development for treating human diseases e.g. anti-hepatitis C virus) results in miR-122\* accumulation, leading to Mdm2 repression followed by elevated p53 protein levels.

Overall, these findings and the effect of the antagomiR-122 on miR-122\* levels could propose a new therapeutic modality and possibly a preventive measure against HCC in high-risk patients such as cirrhotic individuals.

## Epigenetic yardstick for cognitively and emotionally healthy aging as applied to cancer

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The aging process has been linked to the increase of risk for cognitive and emotional decline, which promotes the risk for numerous chronic diseases such as cancer, and a decrease in the physical ability to accommodate them. A genetic and epigenetic signature for this inclined risk has been documented previously in handful reports. However, the ability to predict gene expression and disease risk as well as brain function has not been fully explored.

In a pilot study aimed to test possible cognitive mechanisms that may underlie the elevated depressive symptoms in older adults, 141 individuals (ages 32-85), with no evidence of general cognitive impairments were tested on a novel reversal paradigm and underwent clinical interviews to assess levels of depressive and anxiety symptoms. We found that oldest- older adults have a selective impairment in reversal learning from negative to positive. This impairment positively correlated with levels of depressive symptoms. The results suggest possible cognitive mechanisms that link between impaired ability to reverse negative outcomes and elevated depressive symptoms in older age.

While our pilot study demonstrated the ability to perform the psychological side on this project we will combine our epigenetic skills to design the epigenetics yard stick. We will focus on epigenetic modifications involving cytosine methylation, which have been associated with cognitive decline, a decrease in proapoptotic expression and an increase in oncogenic expression.

We will utilize state-of-the-art technology (i.e. HELPtag) to obtain significant information on epigenomic changes in methylation with aging, and test it in both cross-sectional and longitudinal studies on 9 consequent elderly age groups. These data will be analyzed by assessing the occurrence of age-related cognitive and emotional decline and increasing risk for cancer and its interaction with either supportive or adverse environments (i.e. epigenetic influence).

Our aims are; 1) Cross sectional examination of epigenetic methylation changes across age and their impact on cognition and emotion; 2) Longitudinal examination of epigenomic changes coupled with cognitive and emotional decline and the ability to cope and fight cancer or protective adaptations; 3) Establishing an Epigenetic-Cognitive (EPI-COG) yardstick for evaluation of cognitive and emotional health of the elderly in different environments, and using this yardstick in systematic diseases such as cancer

This study will open the horizons for more specific and functional studies, as previously exemplified by numerous genetic studies, and will lead to a better

understanding of the system biology of the aging brain and cancer disease. Successful interpretation may lead to future treatments and interventions, which will promote cancer free aging.

List of Invited Speakers,  
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