DKFZ-MOST Cooperation in Cancer Research

1st Summer School

Ein Gedi / Israel

November, 23rd – 26th, 2009

Book of Abstracts

dkfz.

MOST

Foreword

The German-Israeli Cooperation in cancer research was founded in 1976 and next year the 33rd annual meeting of our cooperation will take place in Israel.

In 2006, during the 30th Anniversary of the Cooperation, the idea of a Winter School was born. Our aim was to bring together young scientists of cancer research from both countries, Israel and Germany, in a friendly and casual atmosphere where the exchange of ideas could take place. Lectures from well-renowned scientists from both countries give an opportunity to discuss the most recent scientific methods and achievements.

After the successful Winter School in 2008 in Pichl/Austria, the idea to additionally organize a Summer School in Israel was born. As is the case for the Winter School, enough time will be reserved for social activities to enhance interactions amongst both the participating students and scientists.

I look forward to your participation in the 1st Summer School in Ein Gedi.

Wolfhard Semmler

DKFZ-Coordinator Israel-Cooperation

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Abstracts of Lectures

Distinguishing anti- from pro-tumorigenic effects of NF-kB in liver cancer

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A pro-tumorigenic role for NF-κB was indicated by various clinical and animal studies. To the contrary, certain mouse models suggested an anti-tumorigenic role for NF-κB, a paradox that has not been satisfactorily resolved. In our study, we compared two different models of mouse liver carcinogenesis, exposure to the carcinogen diethylnitrosoamine (DEN) and Mdr2-deficiency-based chronic liver inflammation. Our results suggest that the role of NF-κB in liver tumorigenesis is time and context dependent.

Hepatocellular carcinoma (HCC) development in the $Mdr2^{-/-}$ model is slowed down by the IkB supper repressor and a strong selective pressure against expression of the transgenic NF-κB inhibitor was observed during the course of HCC progression. Fifty percent of the tumors arising in IkB transgenic $Mdr2^{-/-}$ mice around the age of 14 months eliminate the expression of the super-repressor, while tissues surrounding these tumors maintain it, pointing to the importance of a cell autonomous NF-κB activity in the formation of these tumors. Despite this apparent strong selection pressure, most of the transgene-free tumors do not exhibit markedly enhanced NF-κB activity, suggesting that the role of NF-κB in this context of cancer development is restricted to an earlier phase of tumor promotion.

Using the super-repressor transgene in an inducible and reversible mode, we timed the window of the NF-κB effect during DEN-induced tumorigenesis to the period of acute carcinogen response. The liver response to DEN involves a temporary NF-κB-dependent proliferation phase, followed by an increased DNA damage response and a subsequent long term cell cycle arrest/senescence, a likely barrier against tumor formation. This cascade following DEN injection did not occur upon NF-κB inhibition in transgenic animals. Yet, unlike $Mdr2^{-/-}$ tumors, carcinogen-induced tumors did not exhibit a selection against the super-repressor, further indicating that the anti-tumorigenic effect of NF-kB is restricted to the early tumor induction phase following carcinogen exposure. These results indicate that different carcinogenic mechanisms may harness NF-kB to either suppress or enhance tumorigenesis.

MicroRNA biogenesis & regulation

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MicroRNAs are important post-transcriptional regulators of gene expression that control physiological as well as pathological processes. Many species ranging from Caenorhabditis elegans to humans as well as many viruses express microRNAs.

MicroRNAs are short (20-23 nucleotides), endogenous, single-stranded RNA molecules that regulate gene expression. Mature microRNAs and Argonaute (Ago) proteins form the RNA Induced Silencing Complex (RISC), a ribonucleoprotein complex mediating post-transcriptional gene silencing. Complementary basepairing of the microRNA guides RISC to target mRNAs which are degraded, destabilized or translationally inhibited by the Ago protein. Proteomic studies have recently uncovered the broad impact of a single microRNA on hundreds of targets. Many cellular pathways are affected by the regulatory function of microRNAs, and most prominently, developmental and oncogenic processes.

While their mode of action has attracted great attention, the principles governing their own expression and activity are only beginning to emerge. Mature, active microRNAs are the product of a complex, multi-step processing pathway that generates the short 21mer from a long primary transcript. Two RNase-III type enzymes, Drosha and Dicer, are involved in cleaving the long precursor into the short mature microRNA. Notably, we have recently identified the effector proteins from the Argonaute family as important players in microRNA biogenesis and regulation, as well, which makes them prime candidates to coordinate microRNA biogenesis and function.

Lastly, the experimental and therapeutic gene knockdown by RNA interference (RNAi) critically depends on the microRNA machinery for the biogenesis and function of the small, ectopically introduced RNAs. These short RNAs (shRNA, siRNA) only contribute the specificity component to the RNAi reaction defining the specific target gene while the cellular proteins have to execute their inhibitory function guided by the small RNAs. Hence, a deeper understanding of the microRNA pathway can also be exploited to enhance the RNAi methodology. As one example, we have been able to transfer the basic insight into the important role of Argonaute proteins to the practical application of RNAi and developed a protocol to strongly enhance RNAi efficiency.

Modelling and Experimental Testing of Cell Cycle Regulation via the ERBB Protein and miRNA Network in Breast cancer

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Overexpression and mutation of transmembrane ERBB tyrosine kinases are adverse prognostic markers in several cancer entities. A causative relation of ERBB signaling with cancer development and progression has been established and, therefore, molecules of the respective pathways are common targets of antibody and small molecule therapies. In breast cancer, ERBB2 is targeted by the monoclonal antibody trastuzumab, however, frequently observed de-novo resistance to this drug requires a thorough understanding of the ERBB signaling network in order to improve prognosis and therapeutic outcome. To this end, we combined computational simulations, experimental testing, and reverse engineering of the ERBB protein and miRNA interaction network in a breast cancer cell system. We first established the technologies and bioinformatic means required to quantitatively analyze ERBB signaling that links extracellular growth-factors with the cell cycle. To this end, we connected ERBB signaling with G1/S transition via two major cell signaling pathways and two key transcription factors, to model an interaction network that allows for the testing of perturbations and the prediction and analysis of induced effects on the phenotype. Individual components were then systematically knocked down in the system and effects on G1/S transition were recorded employing quantitative proteomic and molecular assays. Based on this quantitative data, the original literature-based network could be refined and extended. Additional protein and miRNA components as well as novel connections could be integrated based on experimental validation also of miRNA-gene interactions and the identification of feedback and feed forward loops regulating the signaling network in proliferation as well as in cell migration and invasion. While our understanding of ERBB-signaling is still far from being complete, our data already suggests several proteins and one miRNA (family) as potential novel targets for therapy.

From VEGF to semaphorins: Neuripilin mediated pro and anti-tumorigenic signaling

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Vascular endothelial growth factor (VEGF) is produced in several forms due to alternative splicing. We hypothesized that there may exist receptors that differentiate between different VEGF forms and have identified such receptors. These receptors bound the $VEGF_{165}$ form of VEGF but not the $VEGF_{121}$ form in binding/cross-linking experiments. They eventually turned out to be the products of the neuropilin-1 and neuropilin-2 genes, which were originally characterized as neuronal receptors for axon guidance factors of the class-3 semaphorin subfamily. The neuropilins are expressed in endothelial cells and in many other cell types including many types of cancer cells. These observations suggested that these receptors may play a role in VEGF signal transduction and further suggested that semaphorins may also have a role in the regulation of angiogenesis. The neuropilins were subsequently character-rized as receptors that form complexes with tyrosine-kinase receptors for VEGF and as enhancers of VEGF signaling. However, they also form complexes with members of the plexin receptor family. These receptors serve as signal transducing elements in class-3 semaphorin holo-receptors containing neuropilins and plexins. Since endothelial cells express both plexins and neuropilins, we hypothesized that class-3 semaphorins may regulate angiogenesis. Indeed, semaphorin-3F as well as additionnal semaphorins turns out to be potent inhibitors of angiogenesis. Furthermore, although class-3 semaphorins do not normally affect the proliferation of cultured tumor cells, we found that several class-3 semaphorins were able to inhibit the growth of soft agar colonies from tumor cells that express appropriate semaphorin receptors. We find that although class-3 semaphorins inhibit tumor angiogenesis, inhibition of tumor progression by class-3 semaphorins is primarily due to direct effects on tumor cells rather than due to inhibition of angiogenesis. Our most recent experiments suggest that some semaphorins can be used as systemic drugs that are able to inhibit the development of tumors *in-vivo*. Experiments performed by other research groups suggest that endogenous class-3 semaphorins function as natural secreted inhibitors of tumor progression. Taken together, these results suggest that class-3 semaphorins should be considered as potential drugs for the treatment of cancer.

Molecular analysis of endothelial cells during angiogenesis

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The growth of new blood vessels is regulated by a sequential series of cellular mechanisms which involves 1.) the directional sprouting of outgrowing endothelial cells, 2.) their attractive and repulsive positioning with subsequent network formation and establishment of flow, and 3.) the maturation of the resulting vasculature with recruitment of periendothelial mural cells and acquisition of the quiescent vascular phenotype. This cascade of events is associated with distinct endothelial phenotypes and corresponding molecular signatures designated as tip cell (invading lamellipodia-rich leading cell), stalk cell (following remodeling and lumen forming cell), and phalanx cell (quiescent endothelial cells). Among the vascular receptor tyrosine kinases controlling the angiogenic cascade, the Angiopoietin/Tie ligand receptor system regulates later steps related to vessel maturation and endothelial cell quiescence. Constitutive Ang-1/Tie2 signaling in the adult is required to maintain the quiescent endothelial cell phenotype. In contrast to the well established agonistic Ang -1/Tie2 axis, the functions of the ligand Ang-2 and the receptor Tie1 are much less well understood. Both appear to be context-dependent modulators of Ang-1/Tie2 signaling. Genetic data have solidly established Ang-2 as the functional antagonist of Ang-1/Tie2 signaling. Likewise, circumstantial evidence suggests a role of Tie1 as a signal-enhancing co-receptor of Tie2, but the molecular mechanisms of Tie1 function remain mysterious since Tie1 is to this date an orphan receptor. The presentation will discuss the state-of-the-art of Angiopoietin/Tie function in the cardiovascular system showing 1.) that Ang-2 acts as an endothelial cell produced, thus autocrine-acting modulator of Ang-1/Tie2 signaling, 2.) that Ang-2 controls the responsiveness of the endothelium to exogenous inflammatory, permeability-regulating and angiogenic stimuli, and 3.) that Ang-2 controls mural cell recruitment and differentiation. The presentation will include recent unpublished data unraveling the molecular mechanisms of Ang-2-mediated vascular destabilization and focus on the posttranslational regulatory mechanisms whereby Tie1 modulates Tie2 signaling.

TNF and TRAIL: two very different sides of the same coin

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The interplay between cell death and inflammation plays an important role in cancer development and the understanding of the underlying mechanisms is likely to be instructive for the development of novel strategies to treat cancer. Tumour necrosis factor (TNF) and the TNF-related apoptosis-inducing ligand (TRAIL) form part of the TNF superfamily of cytokines. In addition, they are both capable of initiating signal transduction processes that can result in cell death or inflammation. To do so they at least partially employ the same signalling molecules. However, the sequence of events differs considerably, dramatically affecting the outcome of TNF versus TRAIL signalling. Whereas TNF primarily triggers pro-inflammatory signalling and only secondarily induces cell death by apoptosis or necrosis, the outcome of TRAIL signalling is primarily apoptosis and only secondarily the induction of pro-inflammatory signalling. By using two different unbiased approaches we identified new components of the TRAIL apoptosis signalling pathway and new factors required for TNF-induced inflammatory signalling. To identify novel factors required for apoptosis induction by TRAIL we employed genome-wide RNA interference screening. Amongst other factors, we thereby identified Axin-1 to be required for TRAIL-induced apoptosis. Axin-1 is a known tumour suppressor and negative regulator of Wnt signalling. Intriguingly, Axin-1's requirement for TRAIL-induced apoptosis is independent from canonical Wnt/β-Catenin signalling. Its opposing roles in TRAIL and Wnt signalling pathways indicate that Axin-1 may occupy a key role in balancing apoptosis versus proliferation. Using a modified tandem affinity purification protocol we identified HOIL-1 and HOIP, which together form the linear ubiquitin chain assembly complex (LUBAC) as components of the native TNF-RSC. Overexpression of LUBAC activated NF-κB and ablation of its expression severely hampered TNF-induced gene expression. Consistent with LUBAC-dependent NF-κB activation, its absence sensitised cells to TNF-induced apoptosis. Identification of HOIL-1 and HOIP as novel components of the TNF-RSC allows for a better understanding of the early events of TNF signalling. Insight into LUBAC function and biochemistry gained by examining cells in which known components of the TNF-RSC are individually ablated will be presented.

Programmed cell death (PCD): From single genes and molecular pathways towards systems level studies

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The mammalian cell death network comprises three distinct functional modules, apoptosis, autophagy and programmed necrosis. Together they constitute a network of approximately 200 proteins connected to each other in a non linear fashion via different types of post translational modifications. To establish new pathways within the PCD map and further analyze the network's structure/function organization we currently undertake in the lab two main approaches. One is the classical bottom up approach in which we focus on a group of death –promoting genes isolated in our lab by performing genetic screens (named the DAP genes). The biochemical pathways which link these individual proteins to the particular cell death phenotype which they drive is then identified. One recent study in this respect refers to the DAPk/Beclin-1 connection. We found that DAPk phosphorylates Beclin-1 on T119 located at a critical position within its BH3 domain, and thus promotes Beclin-1 dissociation from Bcl-XL and autophagy induction. These results reveal a substrate for DAPk that serves as one of the core proteins of the autophagic machinery. The other strategy consists of a systems level approach to assess the extent to which the inter-modular connectivity affects cell death performance. To this end, we developed a platform which is based on single and double sets of RNAi-mediated perturbations targeting combinations of apoptotic and autophagic genes. We measure the outcome of perturbations both on the overall cell death responses, by using an unbiased quantitative reporter, and on the molecular responses in the proximity of the knocked-down genes and at distal sites. The double perturbation fitness values are calculated and further analyzed in the context of the changes in the molecular responses to detemine whether seemingly unrelated pairs of proteins are genetically linked. Initial running of this platform in etoposide treated cells identified several levels of connectivity between apoptosis and autophagy . This platform potentially has a wide, general scope of applicability.

Oncogenic signalling networks: relevance to therapy and to biomarker development

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Growth factors and their transmembrane receptors contribute to all steps of tumor progression, from the initial phase of clonal expansion (cell proliferation), through recruitment of blood vessels to growing tumors (angiogenesis), and, eventually to migration and colonization of distant organs (metastasis). Hence, the information relay system involved in growth factor signaling provides potential site for signal interception and tumor inhibition. A relevant example comprises the epidermal growth factor (EGF) and the respective receptor tyrosine kinases, namely ErbB-1/EGFR and HER2, which belong to a prototype signaling module that drives carcinoma development. The extended module includes two autonomous receptors, EGFR/ErbB-1 and ErbB-4, and two non-autonomous receptors, namely: a ligand-less oncogenic receptor, HER2/ErbB-2, and a kinase-dead receptor (ErbB-3). This signaling module is multiply involved in human cancer through autocrine loops involving co-expression of a receptor and one of the many EGF-like ligands, mutations and deletions within the EGFR gene, or amplification of either HER2 or EGFR. Moreover, both EGFR and HER2 serve as targets for several cancer drugs, such as monoclonal antibodies (e.g., Cetuximab and Trastuzumab) and tyrosine kinase inhibitors (e.g., Erlotinib and Lapatinib).

To explain the remarkable oncogenic potential of HER2/ErbB-2, a ligand-less recaptor that forms heterodimers with the other three ErbB proteins, we proposed a network configuration: through a layered organization of ligands, receptor dimers, downstream pathways and transcription factors, the ErbB network tunes and diversifies signal transduction, with HER2 operating as a signal amplifier (see ref. 1).

The network achieves robustness by adopting universal features common to engineered and natural systems: a modular architecture, a common core process, and a dense web of feedback control circuitry. My presentation will concentrate on system controls, which can be divided into two categories: the immediate loops are the domain of post-translational protein modifications, such as receptor phosphorylation, ubiquitinylation and neddylation. One consequence of this phase comprises endocytosis of ligand-receptor complexes, a process evaded by several oncogenic mutants of EGFR (see ref. 2). The late category of system control depends on newly transcribed messenger RNA and micro-RNA molecules. Through coordinated functions, inducible mRNAs and miRNAs terminate expression of the highly oncogenic immediate early genes, such as c-FOS and c-JUN (see ref. 3).

My lecture will highlight examples of tumor evasion from system control. In addition, I will focus on the inevitable fragility of robust signaling networks, as well as propose that system level understanding may help identify Achilles heels amenable for therapeutic intervention.

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Systematic dissection of Wnt signalling in development and disease

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While an increasing number of genomes are sequenced, the function of many genes remains unknown. Genetic screens for phenotypes on the level of the organism have been successfully used to characterize the function of genes and order their action into cellular pathways. RNAi screens now allow a phenotypic characterization of genes on a genome-wide scale and support a systems-level understanding of cellular processes. We have developed approaches to rapidly screen through large libraries of siRNA to identify genes that are required for particular biological processes. We here describe approaches to analyze Wnt signaling pathways using RNAi in Drosophila and human cells.

Many developmental and disease-related processes are mediated by Wnt proteins, which are secreted by specific cells to regulate cellular programs in the surrounding tissue. We have used cell-based RNAi screens in Drosophila to identify factors that act in signal secreting and receiving cells. In such a screen, we identified a novel multi-pass transmembrane protein, Evi/Wls, which is required for Wnt signaling from worms to vertebrates. Loss-of-function alleles in Drosophila have patterning defects that phenocopy *wg* loss-of-function alleles during embryogenesis and imaginal disc development. We showed that Evi is required for the secretion of Wg but not for other ligands. We have expanded such screens using novel assays and independent RNAi libraries to identify components along the secretory route of Wnt proteins. Epistasis screens revealed several other factors required for Wg transduction and we will present current results with a focus on factors required for Wnt secretion.

Live imaging of vascular development in zebrafish

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During embryonic development, the differentiation of endothelial cells and formation of the vascular system are among the earliest events in organogenesis. Serious disruptions in the formation of the vascular network are lethal early in postimplantation, while the maintenance of vessel integrity and the control of vessel physiology have important consequences throughout embryonic and adult life. In recent years, it has become clear that many of the signals implicated in vascular development are reactivated during disease states of angiogenesis such as tissue ischemia, coronary heart disease and tumor-promoted angiogenesis. This has further reinforced the potential medical relevance of vascular development studies. During the past years, the zebrafish has emerged as a superb model for the research of vessel formation *in vivo*. Zebrafish embryos are optically clear, providing non-invasive and high-resolution observation of the entire vascular system at every stage of embryonic development. In addition, the formation and anatomical layout of the fish vasculature are similar to that of other vertebrates, and most of the genes currently known to act as key players in embryonic vascular development are highly conserved in zebrafish. In order to study the early stages of formation of blood and lymphatic vessels, we make use of transgenic zebrafish embryos bearing robust expression of fluorescent reporters in endothelial cells. These embryos can be imaged for up to five days, without developmental delay or loss of viability, using long-term multiphoton microscopy. This new capability has helped elucidate many of the unique behaviors of endothelial cells in developing blood and lymphatic vessels *in vivo*. As most developmental processes are remarkably similar between zebrafish and humans, both in molecular aspects and function, our studies are likely to reveal conserved pathways regulating the development and function of blood and lymphatic endothelial cells in humans.

Cellular and viral microRNAs controlling immune response to stress

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MicroRNAs (miRNAs) are expressed in a wide variety of organisms, ranging from plants to animals, and are key posttranscriptional regulators of gene expression. Virally encoded miRNAs are unique in that they could potentially target both viral and host genes. Indeed, we have previously demonstrated that miRNA derived from 3 different herpes viruses, HCMV, EBV and KSHV down regulates the expression of a host immune gene, MICB. Since MICBV is a ligand for a powerful killer receptor NKG2D, we suggest that the herpes viruses downregulate MICB to avoid immune attack. By questioning why the MICB site is not mutated to avoid such targeting we identified a group of cellular miRNAs which target MICB by using sites which are overlapping with the viral miRNA binding sites. We have also demonstrate that miR-UL112 of HCMV targets the UL114 gene, and we presented evidence that the reduction of UL114 by miR-UL112 reduces its activity as uracil DNA glycosylase but only minimally affects virus growth. In addition, we show that two additional HCMV-encoded miRNAs, miR-US25-1 and miR-US25-2, reduce the viral replication and DNA synthesis not only of HCMV but also of other viruses, suggesting that these two miRNAs target cellular genes that are essential for virus growth. Thus, we demonstrate that MICB play an important role in the life cycle of 3 herpes viruses and that the viral miRNAs control not only the expression of cellular ligand but also the expression of viral proteins.

Activation and inhibition of NK cells by viruses

Frank Momburg

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There is good experimental evidence that infections by many viruses such as herpes simplex virus, influenza virus or the ectromelia poxvirus can be controlled by natural killer cells in mice. Limited evidence also suggests that NK cells play a role in the defense against human herpesvirus infections. Type I interferon and IL-12 secreted by plasmacytoid dendritic cells stimulate NK cell proliferation, cytotoxicity and IFN-□ production in response to viral infections. NK cells, however, also directly recognize various viral proteins that can either have an activating or an inhibitory effect on NK cell activity. We will provide a brief overview regarding known mechanisms employed by mouse and human cytomegalovirus, influenza virus, human immunodeficiency virus, poxviruses and hepatitic C virus to modulate NK cell responses. We will report own recent results demonstrating the activation of NK cells by the paramyxovirus NDV and the poxvirus vaccinia virus through natural cytotoxicity receptors.

The contribution of host-response mechanisms to tumor re-growth following anti-cancer drug treatment.

Yuval Shaked

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Chemotherapy remains one of the main treatment modalities for cancer. Although treatment efficacy is usually achieved, during the treatment-break periods, rapid repopulation of tumor cells and subsequent tumor re-growth are sometimes observed. Our studies demonstrate that cellular and molecular host mechanisms may account for tumor re-growth and the acceleration of potential metastasis following anti-cancer drug treatments. These host response mechanisms promote angiogenesis by the mobilization and recruitment of bone marrow derived proangiogenic cells, which home to treated tumor sites, and induce the formation of new blood vessel capillaries. Here we discuss some of the host response mechanisms to treatment using chemotherapy, radiation, antiangiogenic drugs, and vascular disrupting agents. We focus on the contribution of circulating endothelial progenitor cells to tumor growth and the rapid induction in cytokines and growth factors including VEGF, SDF-1, and G-CSF which are responsible to the systemic angiogenesis process. Furthermore, we show that a blockade of cellular or molecular host responses to anti-cancer drug treatments by neutralizing antibodies, small molecules, or antiangiogenic drugs can increase the efficacy of therapy. These results highlight the possible effect of treatment-induced cytokines on tumor re-growth, and hence blocking such cytokines as possible novel therapeutic targets.

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Information on the Summer School

The German-Israeli Cooperation in Cancer Research was founded in 1976. To date 120 projects have been successfully completed. More information about the cooperation program can be taken from our homepage: www.dkfz.de/israel. The Summer School is jointly organized by the Israeli and German Program Committee.

During the 30th Anniversary in 2006 the idea for a Winter school was born. Our aim was to bring together young scientists from both, Israel and Germany, in a friendly atmosphere where the international exchange of ideas could take place. Lectures from well-renowned scientists from both countries give an opportunity to discuss the most recent scientific methods and achievements. After the successful Winter School in 2008 it was also suggested to hold Summer Schools in the same manner.

The Summer School includes lectures in the morning and afternoon. Additionally social activities are planned for the morning.

Participation is restricted to 20 Students/young Post-Docs.

Wolfhard Semmler

DKFZ-Coordinator Israelcooperation

Location

Ein Gedi –Kibbutz
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German - Israeli Cooperation in Cancer Research

1st Summer School

Ein Gedi / Israel

November, 23rd – 26th, 2009

dkfz.

MOST

Program

Monday, November 23, 2009

afternoon ***Arrival at Kibbutz Ein Gedi***

18:30 h ***Dinner***

19:45 h **Welcome Addresses**
I. Lowi, Ministry of Science and Technology (MOST), Jerusalem
V. Rotter, Weizmann Institute of Science, Rehovot
W. Semmler, DKFZ, Heidelberg

20:15 h **Introduction of Participants**
Students and Lecturers

21:00 h **The archeology of the Dead Sea, emphasizing Ein Gedi**
G. Hadas, Archeological Mission to Ein Gedi

Tuesday, November 24, 2009

06:30 h ***Early Breakfast***

07:00 h ***Social activity (Climbing Nahal David)***

Inflammation and Cancer

11:00 h **The role of inflammation in cancer: lesson from animal models**
Y. Ben-Neriah, The Lautenberg Center for Immunology, Jerusalem

MicroRNA

11:45 h **MicroRNA Biogenesis & Regulation**
S. Diederichs, DKFZ, Heidelberg

Growth Factors

12:30 h **Modeling and experimental testing of ERBB-regulated G1/S transition**
S. Wiemann, DKFZ, Heidelberg

13:15 h ***Lunch***

Angiogenesis

16:00 h **From VEGF to semaphorins: Neuripilin mediated pro and anti-tumorigenic signalling**
G. Neufeld, Technion, Haifa

16:45 h **Molecular analysis of endothelial cells during angiogenesis**
H. Augustin, DKFZ, Heidelberg

Apoptosis

17:30 h **TNF and TRAIL: two very different sides of the same coin**
H. Walczak, Imperial College, London

19:30 h ***Dinner***

20:30 h **Keynote Presentation**
Programmed cell death – from single genes and molecular pathways towards systems level analysis
A. Kimchi, Weizmann Institute of Science, Rehovot

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Summer School

Wednesday, November 25, 2009

06:30 h ***Early Breakfast***

07:00 h ***Social activity (Massada)***

Signal Transduction

11:00 h **Oncogenic signalling networks: relevance to therapy and to biomarker development**
Y. Yarden, The Weizmann Institute of Science, Rehovot

11:45 h **Dissecting signalling networks by genome-wide RNAi**
M. Boutros, DKFZ, Heidelberg

In vivo imaging

12:30 h **Live imaging of vascular development in the zebrafish embryo**
K. Yaniv, The Weizmann Institute of Science, Rehovot

13:15 h ***Lunch***

15:00 h **POSTER PRESENTATIONS by STUDENTS & POSTER DISCUSSION**

20:00 h ***Dinner***

21:00 h ***Social gathering***

Thursday, November 26, 2009

NK cells, innate immunity

09:00 h **Cellular and viral microRNA controlling NK cell activity**
O. Mandelboim, The Lautenberg Center for General and Tumor Immunology, Jerusalem

09:45 h **NK cell activation by viruses**
F. Momburg, DKFZ, Heidelberg

Anti-cancer treatment

10:30 h **The contribution of host response to tumor re-growth following anti-cancer drug treatment**
Y. Shaked, Technion, Haifa

11:15 h ***Light lunch***
departure

Organization

Organizers

German-Israeli Cooperation in Cancer Research

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MOST: Dr. Shlomo Sarig, Nurit Topaz

PhD-Programm

Dr. Lindsay Murrells

Organizing Committee Israel

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