30 Years' German-Israeli Cooperation in Cancer Research 1976 - 2006

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30 Years' German-Israeli Cooperation in Cancer Research

A 30-year anniversary is something to be proud of and offers the opportunity to look back to the beginnings of the German-Israeli cooperation, which started in 1976 initially with three projects. The following phases showed an increase to 10 projects. Since receiving supplemental financing in 1992, a constant number of 14 projects have been ongoing. As of June 2005, a total of 105 projects had been successfully concluded.

The cooperation program has developed very satisfactorily in the course of the past 30 years, as certified by the international review commission in 1997. Outstanding achievements have been made in day-to-day work at the bench and in joint publications: Every year the project partners have reported on the progress of the respective subprojects at the annual meeting of the program committee so as to expand and intensify the cooperation. Indeed, more young scientists are being encouraged to apply for new projects and the priority topics reflect the most recent trends in research, such as stem cell research and a focus on clinical topics.

Several principal investigators contributed to this brochure with reports of their projects. Many thanks go to these individuals and to all the principal investigators and Ph.D. students who have been part of the program. Their achievements and the personal contacts with their project partners have shaped the structure of our cooperation program.

This anniversary brochure also gives a brief look at the history of the cooperation program. All the projects, including ongoing work, are listed in the appendix. The present brochure represents a follow up to our brochure *Cancer Research and Cooperation*, which was compiled in 1999, and summarizes the history and the development of our program. Recently, the literature appendix was also updated to include all publications and reports up to 2004. These documents are available on our homepage (www.dkfz.de/israel).

The coordinators would like to thank the BMBF for funding and the management board of the German Cancer Research Center for their support.

Heidelberg/Jerusalem, March 2006
Prof. Dr. Dr. Wolfhard Semmler Dr. Shlomo Sarig Nurit Topaz

The Initiation of Metamorphosis

Eli Shaaya and Costas Sekeris left their Mediterranean homelands to enter the fascinating world of science in Munich, where the secrets of steroid hormone action were being unveiled at Peter Karlson's lab. After some years of fruitful collaboration, they parted but met again, this time in Heidelberg, where Costas was heading the Division of Molecular Biology of the Cell at the German Cancer Research Center (DKFZ). Eli visited him – two good friends happy to plan their new research project. So did the German-Israeli collaboration 007, (a symbolic number indeed) start (Costas, in his capacity of Division Head, scientifically nurtured in Germany, although a Greek national, in every right represented the German side). The project was based on our common interest in the mode of action of ecdysone, the steroid hormone which induces metamorphosis in dipteran insects.

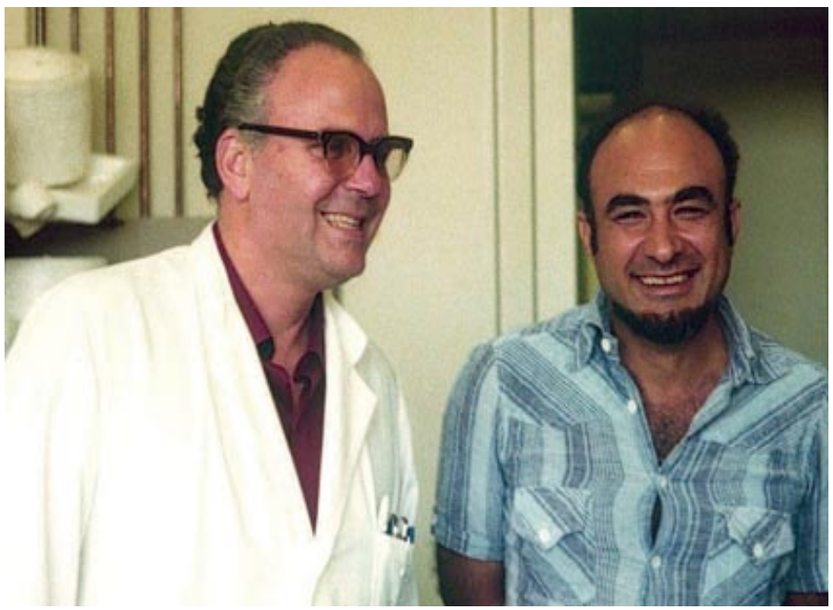
A visible effect of the hormone's action at that stage is sclerotization of the cuticle due to the formation of diphenolic agents, metabolites of tyrosine. A key enzyme involved in their biosynthesis is DOPA decarboxylase, induced by ecdysone in the epidermis cells. Increased synthesis of the enzyme is preceeded by increased availability of DOPA decarboxylase messenger RNA. In our model system, *Calliphora vicina*, during the transition from larva to pupa, ecdysone induces in the epidermis cells giant HnRNA. The question we wished to answer in our project was the relation of the ecdysone-stimulated HnRNA to the observed increase of the DOPA decarboxylase mRNA titer and enzyme, in view of the fact that during metamorphosis two peaks of ecdysone secretion are observed, both of which are followed by increased RNA synthesis.We showed that the changes in RNA synthesis during pupal differentiation are tissue specific but were also observed in *Drosophila melanogaster*, pointing to a general phenomenon connected to the differentiation process. Prior to the HnRNA activation, a quantitative change in DNA methylation and a change in the activity of RNA polymerase II was found. We could show that the initial increase in giant HnRNA synthesis occurs shortly after the appearance of the small peak of ecdysone, but DOPA decarboxylase is induced only after a second peak of ecdysone, induction being a two-step process dependent on both peaks. Our experiments further suggested that only after the second surge of ecdysone there was more genetic information transferred to the cytoplasm.The fact that a-amanitin, the specific inhibitor of RNA polymerase II, injected before pupariation, inhibits RNA synthesis and the induction of the enzyme leads to the conclusion that the appearance of DOPA decarboxylase mRNA after the second ecdysone peak is a result of the stimulation of giant HnNA containing the DOPA decarboxylase mRNA sequence and not of reutilization of preexisting HnRNA. Our results appeared in Gen. Compar. Endocrin. 34:110, 1978 and Z. Physiol. Chem. 360:445, 1979. Shortly before the project was selected, Eli returned to Israel, to the Hebrew University, where most of this work was completed. This project helped to establish his research activities at the University. As he notes, the outcome of the cooperation opened new venues for his research and had a profound impact on his development that led to a full professorship in biology at the Hebrew University. Costas also returned to Athens a few years later to establish an Institute devoted to biological research at the National Hellenic Research Foundation, the experience amassed in Germany being instrumental for the success of his endeavors. Both friends had a hearty reunion in Jerusalem and cherish their long-standing friendship and common research aspirations.

Regulation of synthesis of HnRNA in epidermis cells of insects and its posttranscriptional modification

E. Shaaya, Hebrew University, Jerusalem

C. Sekeris, DKFZ Heidelberg

Period 01.01.1976 - 31.12.1979



Costas Sekeris (left), and Eli Shaaya

Loss of MHC – A Trick to Escape Immune Attack

Three decades of collaboration with Shraga Segal

It all began in the early 70s at Stanford University Medical School in the USA, where Shraga Segal and I met as young postdocs in the laboratory of the ingenious immunologist Hugh O. McDevitt. With the help of synthetic antigens produced by Michael Sela from the Weizmann Institute in Rehovot, McDevitt had just described the exciting discovery that the major histocompatibility complex (MHC) controlled immune responses. During our work in the Stanford lab on MHC control of immune responses, which led to the description of MHC class II molecules, a wonderful friendship developed with Shraga and his family that lasts till today.

In the beginning of the 1980s, when we were back in our home countries Germany and Israel, our mutual interest in the MHC led to a very productive cooperation in which we set out to understand the function of MHC class I molecules on tumor cells. At that time it was known that MHC class I antigens were powerful transplantation antigens that caused vigorous rejection of transplanted organs. However, because organ transplantation usually does not occur in nature, but is an „artefact" generated in the clinic, transplant rejection could not be the physiological role of MHC molecules. The above-mentioned studies by McDevitt were a major breakthrough towards the biological function of the MHC, but only several years later and after our tumor experiments it was described that MHC molecules present peptides from antigens such as virus or tumor antigens, and that these MHC:peptide complexes are recognized by the antigen-specific receptor on T lymphocytes (TCR).

But back to the role of MHC molecules on tumors: Initially, together with the late Michael Feldman at the Weizmann Institute, a charismatic immunologist and brilliant expert on modern art, Shraga Segal was working on several mouse tumors that had lost expression of a particular set of MHC class I genes. Restoration of gene expression by transfection of MHC genes was performed in Heidelberg. At that time gene transfer had just been discovered as a new and powerful technique. The results were surprising. Re-expression of the missing MHC alleles prevented either growth of the primary tumor in mice or metastasis formation. We could show that the immune system was responsible for blockade of growth and metastasis of MHC-transfected tumors. From this, the immune escape hypothesis was developed, stating that loss of MHC molecules would allow the tumors to escape from immune attack. These landmark studies were published in *Nature* as a full article (Wallich et al., Nature 315:301, 1985), and laid the foundation for additional joint publications, but also for numerous studies on this topic by other laboratories.

Shraga Segal (1939 - 2006)

Our fruitful collaboration was accompanied by several visits to the Weizmann Institute and later to Beer-Sheva, where Shraga Segal is now deputy rector of the Ben Gurion University and director of the BGU Cancer Research Center. These visits not only served to design new experiments, but at the same time they very much deepened my understanding for the precarious political situation of Israel.

Over the years, our scientific activities have become much broader. Work from both Beer-Sheva and Heidelberg contributed much to our understanding of the molecular mechanisms of antigen presentation by MHC molecules, of the role of MHC in tolerance and pregnancy, where immunological rejection of the fetus needs to be avoided, and also of the association of MHC with surface receptors for growth factors and its consequences for signalling. Lately, both laboratories have concentrated on the tumor endothelial barrier and strategies for overcoming this barrier for tumor immunotherapy.

Thanks to our friendship and mutual scientific interests, we and the next generation of members from our labs are still continuing to collaborate on MHC and tumor immunology after 30 years of joint research.

Günter Hämmerling

On February 25, 2006 Shraga Segal has passed away at the age of 67 years, much too early. We all mourn for Shraga. He was a very warm-hearted and caring person, always prepared to help his friends and colleagues. As a scientist he was uniquely successful, sparkling with ideas and irresistible in his enthusiasm and optimism. We have lost a good friend and a brilliant scientist. Our thoughts are with his dear wife Mazal and their children

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The immunobiology of tumor metastases & Tumor-associated blood vessel endothelium as a barrier to infiltration of effector immunocytes

S. Segal, Ben Gurion University, Beer-Sheva

G. Hämmerling, DKFZ Heidelberg

Period 01.07.1981 - 30.06.1984 & 01.01.2004 - 31.12.2006

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What Makes Cancer Cells Migrate?

At the time the German partner had published a first manuscript on striking differences in cell shape and adhesion properties of a metastatic versus a non-metastatic subline of a rat pancreatic adenocarcinoma. Based on this publication, Avraham Raz and Avri Ben-Ze'ev, both cell biologists at the Weizmann Institute, with particular interest in mechanisms of cell adhesion, became interested in these tumor cell lines.

We successfully applied for a joint Israeli-DKFZ project and managed to start a most fruitful cooperation on the role of membrane glycoproteins, on the one side, and variations in the cytoskeleton, on the other. This research was based on the suggestion that loss of adhesiveness contributes to the metastatic phenotype, which we explored in the above-mentioned model as well as in the B16 murine melanoma model, where several sublines with significant differences in their metastatic capacity were available. We were able to demonstrate that loss of adhesiveness by itself does not facilitate tumor progression and obtained first evidence that expression of intermediate filaments are essential for the organization of the cytoskeleton with important consequences for the motility of tumor cells. During the project period, Avraham Raz left for an attractive position in the United States. Yet, by the joint effort of Avri Be-Ze'ev and the DKFZ partner the project was successfully completed with 14 publications, including three joint publications. Nonetheless, the fact that the funding period was terminated did not end the cooperation between the DKFZ and the Israeli partner, testified by the fact that there have been an additional three joint publications throughout the past 10 years. In fact, we still are in regular contact and discuss common interests and current issues and both benefit greatly from the other's experience. Conferences in Israel and Germany have been welcome occasions to meet and exchange new ideas and developments, not only about recent scientific issues but also about family and friends.

Escape mechanisms of metastatic tumor variants
A. Raz, A. Ben-Ze'ev, Weizmann Institute, Rehovot
M. Zöller, DKFZ Heidelberg

Period 01.07.1984 – 30.06.1987

Elucidating the Cause of DNA Amplification

The studies conducted together with Sara Lavi focused on the elucidation of initial genetic events occurring in cells after exposure to environmental agents and virus infections. Some of these studies resulted in the development of a novel assay for the analysis of compounds amplifying DNA, by the use of the DNA of infecting adeno-associated virus (AAV), i.e., amplification of the DNA of this virus could be used as a marker for inducible DNA amplification in a variety of cells.

Within this project, there was a close collaboration including exchange of students and post-docs, and later on, a post-doc of my group (Christian Walz) worked for a one-year stay in Lavi's lab (1993/94). During the project period and also thereafter, there were close private relations comprising the families of both partners, including cultural exchange and many fruitful discussions.

The role of DNA-amplification in tumor initiation
S. Lavi, Tel Aviv University
J. Schlehofer, DKFZ Heidelberg

Period 01.01.1986 - 31.12.1988

Monitoring Interleukin Production in Single Cells

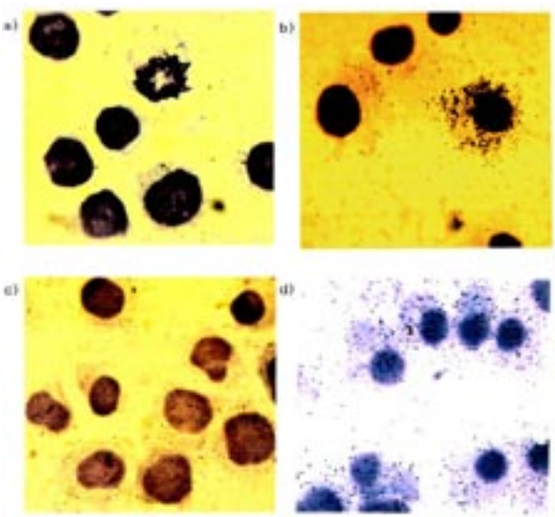
In 1985, the contact between Michel Revel from the Weizmann Institute and our laboratory in Heidelberg was initiated due to our common interest in the biological role of interferons (IFN). At that time our department was headed by Dr Holger Kirchner who had been conducting a most active research in this area since 1975. Michel Revel was also considered an expert in research on IFN and his laboratory had already contributed many exciting details in particular on the possible involvement of IFN in myeloid differentiation. In 1985, for example, his group had cloned the cDNA encoding a cytokine that was named IFN-β_2 and was found to be co-expressed with the „classical" IFN-β by differentiating myeloid cells. In the following year a number of other groups isolated an identical cDNA from other cell types and it became clear that the protein encoded by the IFN-β_2 gene was devoid of antiviral activity. In 1988 this cytokine was named IL-6.

During my post-doctoral research in the laboratory of the late Edward De Maeyer, I had focussed on novel sensitive methods to monitor the presence of IFN. In 1984, I succeeded to visualize for the first time IFN-α and IFN-β mRNA in individual cells by *in situ* hybridization. Our unexpected observation that elicited Michel Revel's interest was the uneven distribution from cell to cell of the autoradiographic signal. Edward De Maeyer and I concluded that even in a given cell population induced to generate maximal levels of IFN, only a fraction of the cells express the IFN mRNA. One of the first aims of the „DKFZ-Israel" co-project was therefore to see if during myeloid differentiation single cells could be detected that expressed IFN or IL-6 mRNA. For this purpose in vitro models were established using the promonocytic leukemia line U937 or freshly isolated human peripheral mononuclear blood cells (PBMC). After one year of skillful experimental efforts conducted by my Ph.D. student Andreas Hartmann we had succeeded to detect IL-6 mRNA in up to 7% of U937 cells induced to differentiate by treatment with phorbolesters (see Fig.). A direct involvement of IL-6 in the differentiation process could not be proven, however, since treatment of U937 cultures with rIL-6 did not elicit any expression of differentiation markers. For IFN-α and IFN-β no direct detection of mRNA was possible. The sensitivity of our *in situ* hybridization approaches turned out to be insufficient even when using ^{35}S-labeled antisense-RNA probes of high specific activity. The expression of these genes could, however, be shown indirectly since Andreas was able to detect the IFN-induced gene 2',5'-oligoadenylate-synthetase by *in situ* hybridization (see Fig.). In view of the limited sensitivity of this technical approach, we started to look for useful additional analytical methods.

In 1988, the „Polymerase Chain Reaction" started a revolution in the whole area of research in molecular biology. Preceded by a reverse transcription (RT) of mRNA into cDNA the „PCR" was rapidly shown to enable the specific detection of only a few copies of any mRNA in cell extracts. With this in mind, Andreas Hartmann started to switch to this new technique and, indeed succeeded to monitor by „RT-PCR" the presence of IFN-α and IFN-β transcripts in phorbolester-treated U937 cells. Similar to IL-6, however, no evidence could be obtained for a biological role of these IFNs in the differentiation process. In addition, in human PBMC no IFN transcripts were detectable during colony-stimulating-factor-induced *in vitro* differentiation from monocytes to macrophage-like cells suggesting that IFN are only expressed during the early differentiation steps „upstream" the monocyte state.

During the course of the project there were unfortunately only few contacts between our laboratories. In retrospect, a possible reason might have been our „negative" results since in previous work using a murine cell line Michel Revel's group had obtained evidence for the involvement of IFN in myeloid differentiation.

Fortunately, in December 1988 after a progress report workshop where all groups participating in the DKFZ-Israel cooperation had met near Tel Aviv in Herzliya, Andreas Hartmann and I had the opportunity to visit Michel Revel's laboratory at the campus of the Weizmann Institute in Rehovot and were very impressed by the campus and the inspiring conversations with Michel and his lab members.



In situ *hybridization of U937 cells expressing IL-6 and 2'5'-oligoadenylate-synthetase mRNA; a, c) untreated, b, d) phorbolester treated U937 cells.*

Agents Controlling the Growth and Differentiation of Primitive Blood Lymphomyeloid/Erythroid Stem Cells

M. Revel, Weizmann Institute, Rehovot
R. Zawatzky, DKFZ Heidelberg

Period 01.07.1987 - 30.06.1990

The Potential of Tumor Necrosis Factor

Both investigators, D. Wallach and I are pioneers in the long successful story of tumor necrosis factor (TNF) research. We both were involved scientifically from the very beginning of defining the TNF bioactivity in serum and supernatants of activated immune cells to the characterization of the molecule, cloning of the gene, analyzing the mechanisms of function, and even to the therapeutic possibilities connected with TNF. While D. Wallach is now recognized internationally as the expert in signal transduction concerning signalling pathways of members of the TNF receptor super-family, I continued to work on the biological functions of the molecule in inflammatory diseases, in sepsis and cancer.

The initial interest in TNF as an anti-tumor agent was based on its potential to necrotize solid tumors in animal models. Soon after discovery of the identity of TNF with „cachectin“, a molecule responsible for the wasting syndrome seen in patients with final stages of cancer or parasite infections, it became obvious that TNF was a very powerful molecule mediating cachexia and endotoxic shock. Intensive research in numerous groups defined TNF as one of the earliest and most important mediators in initiating essential inflammatory reactions for antimicrobial defense. Such a powerful mediator of protection can also cause disease and the outcome hinges on a delicate balance between appropriate and inappropriate induction of this mediator. Furthermore, a complex regulatory network is required to bring the activated immune system back to homeostasis to ensure integrity of tissue and organs.

Mechanisms controlling the response to tumor necrosis factor

D. Wallach, Weizmann Institute, Rehovot
D. N. Männel, DKFZ Heidelberg

Period 01.01.1989 – 31.12.1991

As a result of the intense TNF research around the world, TNF is the first cytokine which has made its way into the clinic to the benefit of many patients. However, it is not the application of TNF as an anti-cancer drug as originally envisioned but rather the neutralization of TNF in situations of chronic inflammation such as rheumatoid arthritis or Crohn's disease.

Our and other's studies of TNF also paved the way to elucidation of the mechanisms for several important aspects of the biology of the tumor cell. Our struggling, together with many other laboratories, to elucidate the molecular mechanisms that define the extent of sensitivity of a given tumor cell to the cytocidal activity of TNF, lead eventually to the clarification of the 'extrinsic cell death pathway' that TNF activates, as well as to clarification of the way this pathway is restrained, through activation of NF-κB, by TNF itself, as well as by aberrations of NF-κB regulation associated with the malignant transformation. The attempts of many laboratories, including ours, to clarify the way by which cells evade TNF-induced killing by shedding of their TNF receptors also led eventually to the identification of TACE, the enzyme that mediates the shedding of many cell surface proteins, including the TNF receptors.

Continuous cooperation of many scientists working on all facets of TNF research made this success possible. Support for such interactions as provided by the *DKFZ-Israel Cooperation* is indeed a very important contribution for this success. However, even more important is the cultivation of personal friendship which among others also requires opportunities to meet each other. This has been provided by the *DKFZ-Israel Cooperation* to David and myself in a very helpful way for which we are grateful.

David Wallach

The Opposing Effects of Interleukin 1

Project Ca44 was funded from 1989 to 1991, with project Ca115 starting in July 2005 – there were also two intermediate projects. I want to focus on the two first-mentioned however, because these are closely related and particularly suited to demonstrate that maintaining contacts in established and successful partnerships is always worthwhile. When Ron Apte first contacted me asking whether I was interested in a joint project, I initially hesitated knowing that his field of expertise was in interleukin 1, where my knowledge was not much beyond textbooks. However, his enthusiasm and our common interest in exploring immune mechanisms for fighting cancer were convincing reasons to find a joint basis of cooperation. With the tools available at the time we could clearly demonstrate that tumor-associated IL-1α reduces tumor malignancy on the basis of potentiation of an anti-tumor immune response – on the other hand, IL-1β potentiates invasiveness.

IL-1 is a pleiotropic cytokine that primarily affects inflammatory and immune responses, but also regulates other homeostatic functions of the body. Knowledge on the diverse effects of IL-1 are still rather limited, which likely is due to the complexity of the system consisting of two agonistic molecules, mostly cell-bound IL-1α and mostly secreted IL-1β, the antagonistic IL-1Ra (receptor antagonist), and two IL-1R (receptor) type I, which transmits signals – and type II, which does not transmit signals and thus serves as a decoy target. Thus, when project Ca44 drew to an end, we both considered a straightforward progression as unlikely to provide clearcut results. However, meanwhile knockout mice for IL-1α, IL-1β, IL-1α and β (double ko), IL-1Ra and IL-1R type I have been generated and the Isreali partner has generated methylcholanthrene-induced sarcomas which are IL-1α, IL-1β, IL-1α and 1β, or IL-1Ra deficient. The availability of this panel of IL-1-deficient mice and tumors allows for the first time a precise analysis of the importance of IL1 in tumor progression and tumor defense, which will provide a solid basis for therapeutic interference. At this stage my interest in the cooperation had grown to the point of filing a joint application proposal myself. Ron Apte is assessing the role of microenvironmental IL-1 on the susceptibility of mice to chemical carcinogenesis, and will characterize the involved mechanisms including also studies on the effects of microenvironmental IL-1 on shaping the repertoire of tumor cells that arise after carcinogen treatment, their invasive potential and immunogenicity. The Israeli group will also perform „criss-cross“ transplantation experiments, in order to evaluate whether IL-1 of host- or tumor cell-origin is important for tumor invasiveness/metastasis and/or interactions between the host's immune system and the malignant cells. The DKFZ group will focus on IL-1α and IL-1β-deficient and overexpressing fibrosarcoma cell lines in conjunction with IL-1R type-I competent and deficient mice to understand the contribution of tumor cell-derived IL-1 in induction of an anti-tumor immune response. The knowledge on the impact of tumor-derived IL-1 on the activation of immune defense mechanisms will be controlled by and translated into preclinical vaccination trials. The same model system will also be used to explore the potential of tumor-derived IL-1 to support tumor invasiveness and neoangiogenesis and whether neoangiogenesis can be inhibited by modulation of IL-1.

The experimetal system evaluated in this joint project is unique in that it enables a concise study on the role of molecules of the IL-1 family in successive steps of the malignant process, i.e. carcinogenesis, tumor invasiveness and metastasis, induction of anti-tumor cell immunity, and application of the knowledge into novel therapeutic protocols taking into account tumor cell- as well as host-derived IL-1. We both are fully engaged in this recently started joint venture and hope we can provide an essential contribution to the role of IL-1 in the interplay between the tumor and the tumor surroundings including the immune system. Needless to say, that after a long record of joint projects the mutual relationship is most well established. Certainly, too, we have come to appreciate our common interests outside of science and always look forward to meeting each other.

Cytokine secretion of tumor cells: Influence on tumor initiation and interaction with the immune system & The impact of host and tumor-derived IL-1 on tumor growth and host defense

R. N. Apte, Ben Gurion University, Beer-Sheva
M. Zöller, DKFZ Heidelberg

Period 01.01.1989 – 31.12.1991 & 01.07.2005 – 30.06.2008

How Do Parvoviruses Kill Tumor Cells?

Jacov Tal, the Israeli investigator, passed away at the beginning of the year 2005, and not only myself but also my family lost a very good friend. During the common scientific project, we studied two different issues concerning parvoviruses. One project was focused on the elucidation of parvoviral nonstructural proteins in parvovirus-mediated oncosuppression, i.e. to understand the role of these proteins in the preferential killing of tumor cells by parvoviruses. In a second project, we studied interactions of helper-dependent parvoviruses (AAV) with autonomous parvoviruses (MVM) concerning complementation and their possible use for recombinant gene therapy vectors. During the „official" cooperation period, there was a very lively exchange of people and ideas, not only between the Israeli group and the DKFZ, but also between Jacov Tal's lab and the Pasteur Institute in Lille (France) where I worked in the 2nd half of the project period. After termination of the project, scientific and private meetings did continue for more than ten years. We met in Heidelberg for the last time just one month before Jacov Tal became ill.

Involvement of the NS genes in the antitumor activity of parvoviruses

J. Tal, Ben Gurion University, Beer-Sheva
J. Schlehofer, DKFZ Heidelberg
Period 01.07.1990 - 30.06.1993

Brigitte und Jörg Schlehofer, DKFZ, Annick Brandenburger, Luxembourg, Jean Rommelaere, DKFZ, Jacov Tal and Michal Mincberg, Beer-Sheva

Carcinogens and Retroviruses – A Dangerous Liaison

In the project supported by the MOS-DKFZ program, the transcriptional regulation of two different retroviruses was analyzed: The Israeli group headed by Prof. Aboud studied the influence of DNA damaging reagents and genotoxic stress on the gene expression of human T-cell leukemia virus type 1 (HTLV-1). In addition, the interaction of apoptosis induction and transactivation of viral and cellular gene expression by the HTLV-1 Tax onco-protein was studied in detail. The cumulative data of these studies showed that Tax prevents DNA damage-induced apoptosis of infected or transduced cells. Such a scenario can explain the pattern of gene expression and clonal activation of malignant cells seen in HTLV-1-positive leukemia patients.

The German team focused on the human foamy virus isolate: the studies conducted in the framework of the cooperation revealed that foamy viruses (FV) are unique among the known retroviruses in directing expression of regulatory and accessory viral genes by a second highly active promoter located in the 3'-end of the *env* gene. This additional promoter is dependent on the FV transactivator and allows switching between structural and nonstructural gene expression. These completely new findings have important implications for construction of FV-derived retroviral vectors and safety aspects related to insertional mutagenesis and activation of cellular genes by FVs and FV-derived gene therapy vectors.

The close relatedness of the topics studied and the constant exchange of ideas and techniques resulted in a high degree of synergy and led to the publication of several joint papers. During the joint project, intense interactions between all members of both groups rapidly developed which led to lively exchanges on both, scientific and nonscientific issues. Long hours of discussion and chatting were shared together. This often resulted in the exchange of ideas on past and present history allowing, based on the differences present, a much more differentiated understanding of the other's viewpoint. In addition to the scientific achievements reached during this joint project, this was a major enrichment for all involved.

Tumorigenic cooperation between human retroviruses, oncogenes, and other carcinogens

M. Aboud, Ben Gurion University, Beer-Sheva
M. Löchelt/R. Flügel, DKFZ Heidelberg
Period 01.01.1992 - 31.12.1994

Lipid Profiles Characterize Tumor Cells

The objective of this research was to investigate lipid/phospholipid metabolism in melanoma cells in culture in response to stimulation with melanocyte stimulating hormone (MSH). In Israel dual-phase cell extraction methods were optimized for the simultaneous isolation of both lipid-soluble and water-soluble phosphate metabolites (phospholipids and phosphomono- and phosphodiesters) for subsequent analysis by NMR. The various ^{31}P-NMR signals from phospholipids and their metabolites that are detectable in extracts were assigned, and the effects of hormone stimulation were studied. In Heidelberg the general influence of cell culture conditions, in particular the concentrations of ethanolamine and glucose in the culture medium, on the NMR-detectable phospholipid metabolite profile in intact tumor cells was investigated.

Both basic culture conditions and hormone stimulation had pronounced effects on the phosphomonoesters involved in phospholipid metabolism. For example, for the human colon carcinoma cell line CX-1, cells cultured under standard conditions showed much lower phosphoethanolamine and much higher UDP-hexose levels than those detected in solid tumors *in vivo*. With the addition of ethanolamine to the culture medium, the phosphate metabolite profile for cultured cells more closely approached that for the *in vivo* situation. The different glucose concentrations present in various commercial media also influenced phospholipid metabolite levels as well as UDP-hexose concentrations, indicating a link between carbohydrate and phospholipid metabolism.

Development of NMR and mass spectroscopic techniques and their application in the investigation of fatty acid and phospholipid metabolism and alterations involved in cellular transduction and malignant growth

H. Degani, Y. Salomon, Weizmann Institute, Rehovot
W. D. Lehmann, W. E. Hull, DKFZ Heidelberg

Period 01.01.1992 – 31.12.1994

In the hormone stimulation experiments peformed in Israel, two strategies were used to quantitate the effects observed: (i) integration of the ^{31}P-NMR spectra obtained from lipid extracts provided direct insight into the molar distribution of cellular phospholipids; (ii) stable isotope tracer experiments with ^{13}C-labeled choline, ethanolamine, or serine allowed the use of ^{13}C-NMR to measure the synthesis of phospholipids. The ^{13}C labeling experiments allowed the quantitation by NMR of both the phosphomonoester precursors and the newly synthesized phospholipids themselves. With ^{31}P-NMR it was demonstrated that stimulation of M2R melanoma cells with MSH led to a decrease in ATP and an increase in cAMP, phosphoethanolamine and, in particular, fructose bisphosphate. In Heidelberg similar stimulation experiments with SK-MEL-28 human melanoma cells indicated an increase in phosphomonoesters without a detectable increase in cAMP.

In the metabolism of fatty acids, the generation of hydroxylated fatty acids has attracted considerable interest since these have the potential to act as markers for general oxidative stress and for the induction of lipoxygenases during chemical carcinogenesis. In the Heidelberg subproject concerning lipid characterization, human saliva samples from patients with oral carcinoma (before therapy) were examined in comparison with samples from healthy controls. A gas chromatography-mass spectrometry (GC-MS) method was developed which provides a position-specific analysis of hydroxylated fatty acids (HETEs and HODEs). This method was applied to demonstrate that patients with oral carcinoma show elevated levels of hydroxylated fatty acids in their saliva. In particular, a strong increase in 5-HETE and 12-HETE was observed, and these products of the enzymes 5- and 12-lipoxygenase may be indicators of inflammatory processes.

In summary, this interdisciplinary project was a stimulating experience for all participants. New personal contacts were established, and new analytical techniques were developed and applied, providing new insights into lipid/phospholipid metabolism in tumor cells *in vitro* and *in vivo*.

A Shared Passion for Growth Factors

The generation of new blood vessels (neovascularization) is an important step during the pathogenesis both of solid tumors and of hematological malignancies. Complex interaction between endothelial cells and leukemic cells and regulation via an array of cytokines indicate a contribution of autocrine and paracrine mechanisms during tumorigenesis. Neovascularization and tumor progression are interdependent processes and are regulated by an equilibrium between angiogenesis activators and inhibitors. Angiogenesis factors like the vascular endothelial growth factor (VEGF) are prognostic parameters for hematological neoplasia and have led to the development of anti-angiogenic therapeutical strategies. A peculiar feature of many soluble growth factors like VEGF and basic fibroblast growth factor (bFGF) is their specific interaction with sulfated polysaccharides (glycosaminoglycans) attached to a protein core. These proteoglycans are situated on the cell surface or integrated in the extracellular matrix (ECM). Binding to these proteoglycans increases the affinity of the soluble factors to their cell surface receptors. Thus, interaction between proteoglycans and VEGF is an initiating step in the cascade which finally leads to the generation of new blood vessels. In our project we investigated the influence of cellular and secreted proteoglycans of human B lymphocytes on ECM components and growth factors situated in the ECM (German part) and of soluble glycosaminoglycans on the biological activity of VEGF and bFGF (Israeli part).

During this project we characterized for the first time the proteoglycans synthesized by human B lymphocytes and corresponding leukemia cells. These proteoglycans albeit in different forms are expressed on the cell surface and released into the environment. While the surface-expressed proteoglycans specifically bind to the ECM component laminin thus mediating adhesion of B lymphocytes to ECM, the soluble proteoglycan was able to inhibit C1q, the first component of the complement cascade. Although looking promising in the beginning we could not clearly define an interaction of various B cell proteoglycans with VEGF or bFGF under stringent binding conditions. At the same time G.Neufeld continued his work on VEGF isoforms and defined their ECM binding capacity, found new VEGF receptors on tumor cells, and described more closely the requirements of VEGF for heparan sulfate interactions. New insights in structure and functions of human B lymphocyte proteoglycans and the biology of VEGF were gained during this project.

Now after almost 10 years, both groups still work in these fields which received growing interest of the biomedical scientific community. While we concentrate our work on factors which favor the *de novo* expression of surface expressed structures of endothelial cells involved in adhesion and migration, Gera Neufelds group is active in studying inhibitors of angiogenesis. During visits in Germany and Israel we had the opportunity to get to know each other both in our professional and private environments.

Shopping strawl with Gera Neufeld (on the right) in a Druse village

Growth factor regulated interaction between leukemias/ lymphomas and endothelium

G. Neufeld, Technion, Haifa
R. Schwartz-Albiez, DKFZ Heidelberg

Period 01.07.1993 – 30.06.1996

A Pacemaker of Inflammation

The response of the body to cancer has many parallels with inflammation and tissue regeneration. A link between cancer and inflammation/regeneration is the arachidonic acid metabolism that generates in close association with the formation of reactive oxygen species (ROS) a plethora of biologically lipid mediators, so-called eicosanoids, which coordinate the complex tissue reactions involved in these processes. As autocoids, the biological activities of eicosanoids are primarily determined by their biosynthesis via the cyclooxygenase (COX), the lipoxygenase, and the monooxygenase pathways and the availability of free arachidonic acid as a substrate, which is provided through phospholipase A_2-catalyzed hydrolysis of phospholipids. The expression and activity of these pace-making enzymes are strictly regulated under normal conditions, transiently up- or down-regulated during irritation and tissue regeneration, and permanently deregulated during carcinogenesis. The major objective of the joint project was to identify regulatory pathways of activation of cytosolic phospholipase A_2 ($cPLA_2$), which is the major enzyme involved in the release of polyunsaturated fatty acids, in particular arachidonic acid, and to analyze COX isozyme expression in keratinocytes in culture and epidermal tumors.

Regulation of gene expression in tumor growth: overexpression of prostaglandin H synthase isozymes as potential markers for epithelial tumors

U. Zor, R. Goldman, Weizmann Institute, Rehovot
F. Marks, G. Fürstenberger, DKFZ Heidelberg

Period 01.01.1995 – 31.12.1997

In a fruitful cooperation comprising the exchange of tools, experimental know-how, and repeated personal contacts and discussions we were able to show that the increase of $cPLA_2$ activity and its translocation to the perinuclear membrane are associated with a transient increase of intracellular Ca^{2+} and the generation of ROS that are both causally related to the liberation of arachidonic acid from phospholipids providing the substrate for COX-catalyzed prostaglandin synthesis. With respect to the COX isozyme expression in mouse and human skin we found COX-1 to be constitutively expressed to a similar extent in normal, regenerating, or neoplastic skin. COX-2 mRNA and protein were absent in normal epidermis, transiently induced by inflammatory and mitogenic stimuli and permanently overexpressed in basal keratinocytes of both premalignant and malignant lesions in mouse and human skin. The suppression of COX-2 activity was associated with an inhibition of tumor formation in mouse skin induced by the initiation/promotion protocol. This data points to a causal relationship between aberrant COX-2 expression and tumor development in this model system.

Koffler Accelerator on the campus of the Weizmann Institute of Science, Rehovot

Breaking Complement Resistance of Tumor cells – A Novel Approach in Cancer Immunotherapy?

Destruction of cancer cells by the cytolytic complement system is hampered by several extracellular and intracellular resistance mechanisms. Between 1996 and 2002 Profs. Zvi Fishelson of Tel Aviv University and Michael Kirschfink of the University of Heidelberg investigated together the mechanisms supporting tumor complement resistance and identified several factors which permit malignant cells to escape the humoral immune response of cancer patients. Complement resistance is achieved by overexpression of membrane-associated complement regulatory proteins, such as CD55 (DAF, Decay-Accelerating Factor), CD46 (MCP, Membrane Cofactor Protein), and CD59 on tumor cells. These proteins block the process of complement activation and prevent formation of the membranolytic complement attack complex C5b-9. As shown by this research, to produce a protective surrounding microenvironment, a tumor cell can also secrete soluble complement inhibitors and express on its surface an ecto-protease that degrades complement proteins or an ecto-protein kinase that impairs by phosphorylation the activity of complement components. Elevated sialic acid expression was also shown to confer complement resistance to cancer cells and has been correlated with increased metastatic activity in certain tumors.

Molecular basis of the resistance of tumor cells to complement-mediated lysis & Sensitization of human tumor cells to complement-mediated lysis

Z. Fishelson, Tel Aviv University
M. Kirschfink, Institute of Immunology,
University of Heidelberg

Period 01.07.1996 – 30.06.1999 & 01.07.1999 – 30.06.2002

Tumor cell protection from complement can also be augmented upon stimulation with cytokines, hormones, drugs, or even with sublytic doses of complement and other pore-forming molecules, such as perforin. As also demonstrated in this collaborative research, tumor cells become susceptible to complement-mediated lysis upon neutralization of their membrane-associated complement regulatory proteins with specific antibodies or gene silencing strategies. Inhibitors of proteases or protein kinases and removal of surface sialic acid residues, all lead to additive complement sensitization effects on human leukemia and carcinoma cells. It is anticipated that the novel results obtained in these joint projects and the continuing collaborative research will permit a detailed assessment of the significance of the molecular mechanisms supporting complement resistance of tumor cells and, most importantly, may also lead to development of a novel approach in cancer immunotherapy.

This research started in 1996 as a scientific collaboration and quickly developed into a personal friendship between Zvi Fishelson and Michael Kirschfink. It was fuelled by several exchange visits and trips to Israel and Germany and frequent meetings at international conferences. Multiple shared publications have been achieved in this joint project and this scientific collaboration is still going on.

Zvi Fishelson (left), and Michael Kirschfink

The Secret Functions of HBV Protein X

I became interested in HBV mainly when I learned that this virus causes liver cancer in humans. The underlying mechanism was not known and as a matter of fact remains elusive even to date. Being familiar with the mechanisms of virus-related cancer induction in mice, I was attracted by the model of HBV. My working hypothesis was, at that time, that the enhancer of HBV might play a key role in insertion activation of cellular proto-oncogenes. This led us to the discovery of the HBV enhancer. Later we examined the role of the X gene in this process. During one of the annual meetings on HBV the poster from Claus Schröder's lab caught my interest in which they described isolation of an HBV unique mutant from liver cancer. This was astonishing, since the detected mutation was localized at a very strategic region, between the enhancer and the X-gene open reading frame – thereafter I was looking for an opportunity to collaborate with Schröder's group on this matter. Fortunately, this opportunity was soon provided under the auspices of Israel-DKFZ joint program. We both were interest in finding a link between the functions of tumor suppressor p53 and the X protein of HBV. The working hypothesis was that the X-gene variants detected in liver cancer may fall into a distinct category of function-mutants, antagonizing the function of p53. At that time tools to measure apoptosis were not much developed and the large number of X mutants demanded laborious work. Therefore, although the hypothesis is simple, progress was much slower than anticipated and four years of collaboration ended with a number of open questions rather than a specific conclusion. *Y. Shaul*

Functional interaction of px of HBV with the tumor suppressor p53

Y. Shaul, Weizmann Institute, Rehovot
C. Schröder, DKFZ Heidelberg

Period 01.07.1996 – 30.06.1999

There is not much to add to the friendly lines of Dr Yosef Shaul, known to people working with him also as Yossi. The issue that brought us together was the said little X protein of the hepatitis B virus. One of the features making it a difficult object to study is that this protein appears to have multiple functions. The idea that there are different forms of the protein with distinct roles is attractive and is actually being pursued. Yes, we did not achieve a joint publication as a visible justification of the support we got but there are many other reasons to consider this cooperation a success. Aside from the benefits of stimulating discussions and exchange of unpublished data, I cherish my visit to the Weizmann Institute. Situated within a beautiful public park area it is integrated in the lively community of Rehovot. Compared to the funding of the DKFZ, the proportion of private money running this excellent institution is amazing. During my visit in Dr Shaul's laboratory I was impressed by the broad spectrum of research and enjoyed to talk to his students about their ongoing work and future plans. I also appreciated that the students showed me around, all the way up to Tel-Aviv, and linked this nicely with an introduction to the history of their young state. Dr Shaul and I still meet on events like the recent meeting on Molecular Biology of Hepatitis B Viruses in Heidelberg, and it feels always as if our last meeting has just been a short time ago. *C. Schröder*

Dwek Campus Center at the Weizmann Institute of Science, Rehovot

Guided Missiles Against Cancer Cells

In 1996, Zelig Eshhar and co-workers at the Weizmann Institute constructed a miniature guided missile for destroying cancer cells which combined the binding properties and specificity of an antibody with the killing power of a cytotoxic T-cell. This was accomplished by fusing the binding domains of an antibody to the cytoplasmic domain of a key component of the T-cell receptor complex responsible for signal transduction. Zelig Eshhar´s group demonstrated that the chimeric "T-body" was able to target and kill tumor cells that displayed the target molecule recognised by the antibody.

Melvyn Little and his group at the DKFZ used a different approach for harnessing the killing potential of T-cells for treating cancer. They combined two different antibodies in one construct: one antibody bound a tumor-associated target and one arm bound to the T-cell receptor. The tight contact of the antibody-bound cells resulted in tumor cell lysis.

Both the T-body approach and the bispecific antibody approach required the use of recombinant antibodies that could target tumor cells. The DKFZ group had already developed methods to obtain recombinant monoclonal antibody DNA both from antibody-producing cells (hybridomas) and from human antibody libraries, which they generated from the antibody gene repertoire of human lymphocytes or by gene synthesis. A cooperation was therefore started between the two groups in the framework of the DKFZ-Israeli programme to arm T-bodies with antibodies from the DKFZ group. Since both sides were interested in the treatment of lymphomas, an antibody targeting malignant B lymphocytes was chosen for the construction of a T-body with this specificity.

The intended mission of the chimeric "T-body" was to find and destroy tumor cells that had survived treatment with conventional chemotherapy. In vitro tests with the T-body showed that this was indeed feasible. In practise, this approach has to contend with considerable technical difficulties such as the efficient transfection of T cells with viral vectors and the ex-vivo cultivation of the T-bodies. In addition, the regulatory hurdles for their use in clinical trials are considerable. For these reasons, the DKFZ group decided to remain focused on the development of bispecific antibodies for recruiting T-cells and natural killer cells to kill tumor cells. For both sides, however, the interaction of the two groups provided a stimulus for the development of novel immunotherapeutic approaches for the treatment of cancer.

Redirecting effector lymphocytes to lymphomas using chimeric receptors with antibody specificity

Z. Eshhar, Weizmann Institute, Rehovot
M. Little, DKFZ Heidelberg

Period 01.07.1996 – 30.06.1999

Melvyn Little

Enhanced Kinase Activity – A General Feature in Viral Carcinogenesis?

Increased tyrosine phosphorylation is a common feature of many cancers. Up-regulation of specific receptors or/and enhanced tyrosine kinase activity concomitantly elevate intracellular phosphorylation of many downstream regulatory proteins, which guarantees the maintenance of unscheduled DNA synthesis and cell proliferation. In the laboratory of Alexander Levitzki, defined synthetic compounds have been designed which can efficiently block tyrosine kinase activity (tyrphostins) and in turn the proliferative phenotype.

In the case of papillomavirus-linked diseases, alterations of epidermal growth factor (EGF)/insulin-like growth factor I (IGF-I) signal transduction and in turn increased tyrosine phosphorylation seem to play a pivotal role during multistep progression toward malignancy. For example, the bovine papillomavirus type 1 (BPV-1) E5 oncoprotein exerts its transforming function through constitutive activation of growth stimulatory pathways via interaction with platelet-derived growth factor and EGF receptors. Furthermore, both BPV-1 E5 and the corresponding homolog of the human papillomavirus (HPV) type 16 can cooperate with ectopic EGF receptor expression in cell transformation assays. This supports the notion that enhanced tyrosine kinase activity is apparently a general feature in viral carcinogenesis because elevated expression of EGF/IGF receptors has been reported in a wide proportion of papillomavirus-induced malignancies. A suitable model system, in which enhanced intracellular tyrosine phosphorylation signaling can be studied in the context of viral transcription and transformation, is provided by BPV-1-transformed mouse fibroblasts.

Characterization of the biological effects of EGF/IGF kinase inhibitors on the transcriptional regulation of human papilloma viruses in immortalized keratinocytes and cervical carcinomas

A. Levitzki, Hebrew University, Jerusalem
F. Rösl, DKFZ Heidelberg

Period 01.07.1996 – 30.06.1999

Here, E5 is considered the main oncoprotein because mutations within the ORFs of E6 and E7 (encoding the major HPV-16/18-transforming proteins) have only marginal effects in focus formation assays using rodent cells as recipients. Similar to premalignant HPV-positive keratinocytes, BPV-1 persists as multicopy episomal nucleoprotein complexes in transformed cells.

In our study, we could show that the tyrphostin AG 555 can selectively suppress BPV-1 transcription through MAP kinase pathway activation and binding of phosphorylated Jun/ATF-2 at a novel identified intragenic regulatory sequence. We also demonstrated that AG 555 affects the transcription of the major regulatory viral protein E2 by shifting the ratio between E2 transactivator in favor to the repressor function. These data indicate that fine tuning of BPV-1 gene expression in transformed cells is regulated by tyrosine phosphorylation.

During our last collaboration I met Alex Levitzki several times, not only in Heidelberg, but also in Jerusalem. I became acquainted with his wife, who is also working in science. For me it is always a pleasure to meet persons like him - who do, despite the seriousness of our scientific business - never forget to laugh and to enjoy a nice evening. Moreover, an indication for a good personal relationship is finding other topics than science when spending the evening together and thus realizing that one shares many other interests as well. Although our last common project ended a couple of years ago, we are still in contact and I really know that with Alex I have a good friend in Israel. I also appreciated his hospitality, especially when I visited Jerusalem together with my fourteen-year-old son last year.

The German-Israeli collaboration project guarantees not only high-quality research, but also ensures a good personal relationship between the scientists.

Frank Rösl

The Role of p53-Mutations in Chemoresistance

The main objective of the joint project was to investigate the molecular biology of p53-mediated apoptosis with special emphasis on its relationship to the killing of cancer cells by chemotherapy and on the relationship between p53 and the expression and activity of the CD95/Fas/APO-1 death receptor.

The most commonly occurring loss of a proapoptotic regulator through mutation involves the p53 tumor suppressor gene. The resulting functional inactivation of the p53 protein occurs in more than 50% of human cancers and results in the failure to trigger apoptotic pathways and resistance of cancer cells to chemotherapy. We have shown that wild-type (wt) p53 directly transactivates the CD95 gene via an intronic binding site (Müller et al., J.Exp. Med.188:2033, 1998).

The aim of this study was to investigate the impact of p53 mutations on the regulation of the CD95 gene and on the responsiveness of hepatoma cells towards induction of apoptosis. We found that wt p53 has a stimulatory effect on CD95 gene activity, whereas most of the mutant p53 proteins investigated are not able to transactivate the CD95gene. This may explain why mutations in the p53 gene contribute to tumor progression and to resistance of cancer cells to chemotherapy. Apparently p53 mutants with defective apoptotic properties are selected during hepatocarcinogenesis.

Due to the fact that their fields of expertise were different (p53 M. Oren, apoptosis P. Krammer and M. Müller-Schilling), both laboratories could successfully study p53 and its mutants.

The guardian of the genome, p53, and death receptor CD95

M. Oren, Weizmann Institute, Rehovot
P. Krammer, DKFZ Heidelberg

Period 01.07.1999 – 30.06.2002

The Cell's Response to Carcinogens

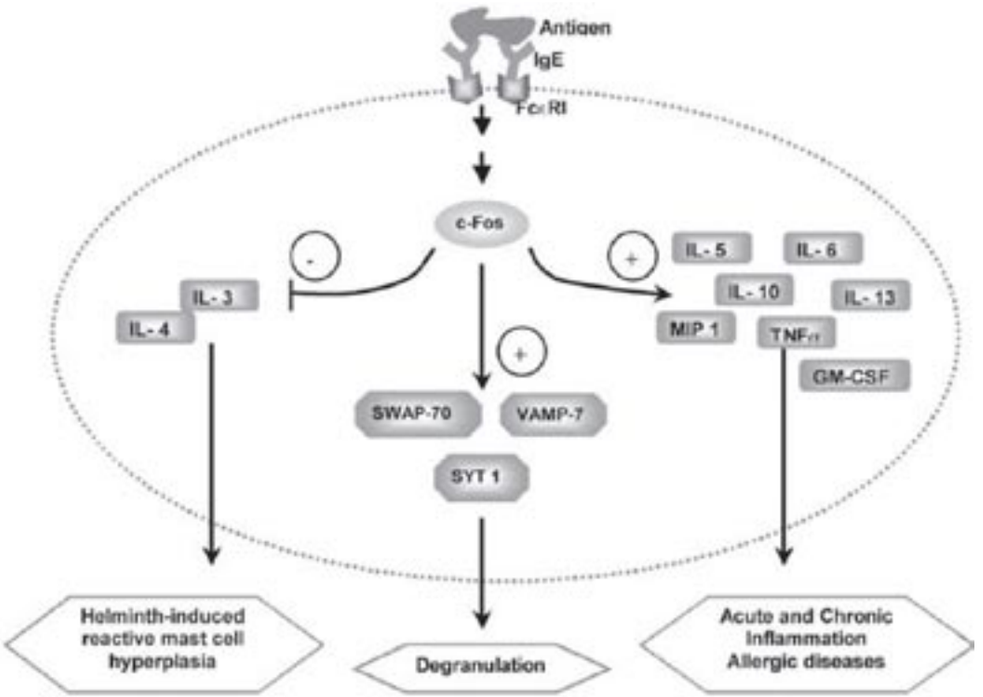
A tight balance of regulatory processes that lead to cell proliferation, differentiation, or programmed cell death (apoptosis) determines the integrity of an organism and it is commonly accepted that dysregulation of components of this regulatory network results in genetic programs allowing the cell to acquire tumor-specific functions. These processes are controlled by synergistic action of a large number of specific target genes (gene programs), whose expression are regulated by binding of so-called transcription factors to appropriate DNA binding sites in such genes. In the joint project supported by the MOS-DKFZ program, the function of specific endpoints of such signalling pathways, the transcription factors AP-1 (members of the Jun and Fos protein families) and microphthalmia (MITF), in the regulation of cell proliferation and apoptosis in response to UV light and chemical carcinogens was explored.

The German group headed by Professor Angel employed fibroblasts from genetically modified mice (so-called knockout mice) lacking AP-1 members (c-Fos, c-Jun, JunB) to define genetic programs controlled by AP-1 in response to carcinogens. Depending on the deleted members, mutant cells became either hypersensitive (enhanced apoptosis) or resistant (loss of apoptosis), and critical target genes, such as CD95-L, as well as important regulators of the cell cycle could be identified.

The Israeli team headed by Prof. Razin focused on the function of AP-1 members, particularly c-Fos, in lymphoid cells, which are physiologically relevant targets of apoptosis and are the most extensively utilized cell type to study molecular mechanisms of cell death, e.g. during activation and response to therapeutic drugs. By comparing mast cells (which represent the major players in the allergic response) isolated from wildtype and *c-fos* knockout mice, a variety of c-Fos regulated functions including proliferation, degranulation capability, and the regulation of cytokine expression were identified.

The success of this project, which laid the basis for a still ongoing collaboration between the two labs, is evident from a number of publications including a well-recognized joint paper. Success was based on an intensive exchange of ideas and reagents, resulting in a high degree of synergy, which was optimized by a three-month visit of Dr. Razin's Ph.D. student in the Heidelberg lab. In addition to scientific issues, importantly, this visit as well as personal visits of the PIs in Israel and Germany strongly fostered personal friendship and allowed to gain novel and invaluable insights of German and Israeli history, culture, and daily life.

Positive and negative regulatory functions of the transcription factor c-Fos/AP1 in mast cells in early immune response (Lee et al [2004] J Immunol 173, 2571)



Identification of cellular pathways mediating cell death in response to radiation and genotoxic agents

E. Razin, Hebrew University, Jerusalem
P. Angel, DKFZ Heidelberg

Period 01.07.1999 - 31.06.2002

Bone Protein Expression – A Prerequisite for Skeletal Metastasis?

Skeletal metastasis of cancer is a long and painful type of disease. Currently used clinical measures such as surgery, radiotherapy, and certain drugs can stop the progress but not cure the disease. Our aim was to contribute to the understanding of the pathogenesis as well as to the treatment of skeletal metastasis and therefore we asked a simple question based on the following observation: Certain tumor cells are known to produce proteins which occur almost exclusively in the skeleton. Examples are the proteins osteopontin and bone sialoprotein, which constitute a large percentage of the extracellular matrix of the skeleton. Could it therefore be that the production and secretion of these proteins are instrumental in and necessary for skeletal metastatic processes to occur? We followed this hypothesis by an approach which has been named 'temporary knock down of genes'. Following this tactic the production of a respective protein from a given target gene is suppressed by a small stretch of DNA (named antisense oligonucleotide, ON) which is constructed to interfere with the cellular transcription/translation machinery for the gene of interest. As a result, the protein expression is reduced and the cellular properties can be investigated in the (relative) absence of the respective protein. Thus we thought if osteopontin and bone sialoprotein were indeed instrumental and necessary for skeletal metastasis to occur, their temporary knock down should inhibit the formation of skeletal metastasis.

A major obstacle then was the delivery of these antisense oligonucleotides to the target cells. One of the major limitations for oligonucleotides gene therapy is their poor cellular delivery. A therapeutic gene can be delivered to the cell and nucleus by viral vectors, which are very efficient in transfecting the cells but might be unsafe for the patient, or by non-viral vectors, which are safer carriers but less efficient. From the studies on gene delivery vehicles, it is clear that there is a need for better delivery systems. These systems should be safe and designed to achieve high intracellular expression levels of the gene product in-vivo as well as to foster better compliance by the patient, increase resistance to nuclease degradation, and ensure continual gene uptake at the tissue site with prolonged duration of expression. Gene and ON therapy thus far has focused on a number of delivery techniques that have departed conceptually from pharmaceutical strategies used to investigate optimal delivery approaches for other therapeutic agents. A careful pharmaceutical approach for discovering gene delivery systems as part of a therapeutic strategy was our aim by encapsulating the ON in a non-viral delivery system. This was achieved by encapsulating the oligonucleotides in biocompatible and biodegradable polymeric nanospheres.

Our subsequent experiments showed largely that these assumptions were correct. After using certain antisense oligonucleotides the expression of osteopontin and bone sialoprotein was distinctly diminished and thus treated breast cancer cells lost a small part of their capability to proliferate, a larger part of their ability to form colonies, and a considerably large part of their ability to migrate towards skeleton-derived cells. Finally, in a rat model the formation and growth of osteolytic metastasis was distinctly suppressed thus demonstrating that the two proteins are indeed necessary for skeletal metastasis to occur and thus could be the start for finding a therapeutic means against this disease.

A special aspect of this cooperation was due to the fact that the Ph.D. student of the DKFZ group was a Palestinian from Gaza. He had been selected as most suitable from a series of candidates, but how would this selection influence the cooperation between the two PIs? Would it be a hindrance for a cooperation that still had to prove its working benefit? The first joint meeting was to take place in Heidelberg and this occasion would bring forward the answer to this question. However, after the relatively shy introduction of the Palestinian student the remarkable answer was 'I have a Palestinian student, too, working in my lab!' From there on both of us knew that this fact would not hold back the cooperation. On the contrary, the Palestinian student working at the Hebrew University got also involved in the cooperation and later became coauthor of a joint publication. Most recently, the two former Palestinian students who in the meantime became Ph.D.s, respectively, have joined in plans on future trilateral cooperations.

On Michelstadt christmas market: Professor Martin R. Berger, Dr. Irene Berger, Shimona Golomb, and Professor Gershon Golomb

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Development and evaluation of non-viral antisense oligonucleotide and gene-controlled delivery systems for the treatment of mammary carcinoma and bone osteolysis

G. Golomb, Hebrew University Jerusalem
M. R. Berger, DKFZ Heidelberg

Period 01.07.1999 - 30.06.2002

Heparanase – A Novel Cancer-Specific T-Cell-Target?

In a long-standing German-Israeli cooperation between Prof. Israel Vlodavsky and Prof. Schirrmacher, heparanase (Hpa) was identified as an important molecule in cancer metastasis. The human genome contains only one gene coding for heparanase and the sequence of the gene product is known. The objective of our latest cooperation project (CA 90/0182) was to evaluate heparanase as a promising target for new therapies including immunotherapy. To analyze CD8 T cell responses, more than 30 nonamer peptides that fit into HLA/A0201 molecules were selected based on the sequence on the human heparanase gene. Three peptides were synthesized for HLA-A2 tetramers and also to pulse autologous dendritic cells from breast cancer patients to evaluate immune memory T cell responses from bone marrow derived cells. We were able to demonstrate the existence in breast cancer patients of Hpa-specific T-lymphocytes by FACS-flow-cytometry using Hpa peptide MHC class I tetramers. In a high proportion of breast cancer patients we detected memory T cell responses in ELISPOT assays to Hpa-derived HLA I restricted peptides. These responses lead to production of interferon-γ and to the generation of antitumor cytotoxic T-lymphocytes.

Volker Schirrmacher

Heparanase-specific T cells were not detected in healthy donors but only in cancer patients. Our results demonstrate that Hpa induces an equal or even stronger immune response in breast cancer patients than the previously described tumor-associated antigens MUC-1 or Her-2/neu. Since Hpa overexpression is a characteristic of metastatic cells, Hpa is an interesting new tumor-associated antigen to target cancer cells with metastatic potential. Recent results have shown that soluble heparane sulfate (HS), a product of the degradation of heparan sulfate proteoglycanes (HS-PG) by Hpa delivers activating signals to macrophages and induces functional maturation of dendritic cells, thus contributing to the generation and maintenance of T cell immune responses. HS was identified as an endogenous stimulator of Toll-like receptor 4 (TLR-4).

An important basis for this successful collaboration has been a long-standing trust and friendship between the two cooperating partners.

Tumor-metastasis-associated heparanase: A newly discovered target recognized by memory T-lymphocytes of breast-cancer patients

I. Vlodavsky, Hadassah University Hospital, Jerusalem
V. Schirrmacher, DKFZ Heidelberg

Period 01.07.1999 – 30.06.2002

Triggering NK-Cell Killing of Tumor Cells

Natural Killer (NK) cells destroy virus-infected and tumor cells very efficiently. The NK killing activity is regulated in large part by the expression of NK inhibitory receptors that recognize MHC class I proteins expressed on the cell surface of target cells. In addition, it was recently demonstrated that the killing of tumor and virus-infected cells is also regulated by NK activating receptors that include mainly the NKp30, NKp44, and NKp46 receptors collectively termed Natural Cytotoxicity Receptors (NCR). In a DKFZ/MOS project conducted by Ofer Mandelboim from the Lautenberg Center for General and Tumor Immunology, Jerusalem, and Frank Momburg from the DKFZ tumor cell-bound molecules that interact with the NCR were studied. The investigation of activating receptors on NK cells and their binding partners on tumor cells is of great interest because there is hope that NK cell lysis of tumor cells can be improved by enhancing the expression of activating binding partners.

We demonstrated that both the NKp44 and the NKp46 receptors can interact with influenzaviral hemagglutinin protein and that this interaction leads to the killing of infected cells by NK. Soluble immunoglobulin fusion proteins of NKp46, NKp44 and NKp30 were utilized for the search of non-viral ligands that are able to trigger the NK lysis of tumor cells. These important tools were produced in a joint effort of the Israeli and German groups. We found that phospholipase C treatment of tumors cells abolished their reactivity with NKp46-Ig and NKp30-Ig. Consistently, phospholipase C treatment of carcinoma cells reduced their susceptibility to human NK lysis. This line of research is being continued after the end of the grant period in the hope to identify glycosyl phosphatidyl inositol-linked NCR tumor cell ligands.

Other mechanisms that control NK cell activities were additionally studied in the course of this project. We demonstrated the existence of a novel class I MHC independent inhibitory mechanism of human NK cell killing that is mediated by the CEACAM1 adhesion molecule. We have shown that the non-classical MHC class I molecule HLA-G is found in complexes on the cell surface and that these complexes efficiently inhibit NK cell activity via the interaction with the LIR1 inhibitory receptor. We demonstrated that overexpression of a particular NK inhibitory receptor (such as KIR2DL1) can be harmful and might lead to a possible autoimmune manifestation. Together we have investigated an additional topic dealing with antigen presentation in the MHC class I pathway. The accessory molecule tapasin functions to optimize peptide loading of class I molecules in the endoplasmic reticulum. We found that tapasin influences the peptide cargo of human HLA-B*4402 class I molecules and thereby enhances their NK inhibitory capacity.

Both partners enjoyed the lively interaction throughout the grant period that resulted in the frequent exchange of ideas and reagents. During mutual visits in Germany and Israel an excellent personal relationship was established which led to plans to continue the fruitful collaboration in future projects.

Identification of the NKp46 ligand: A ligand that is involved in the recognition of virus-infected and tumor cells

O. Mandelboim, Hebrew University, Jerusalem
F. Momburg, DKFZ Heidelberg

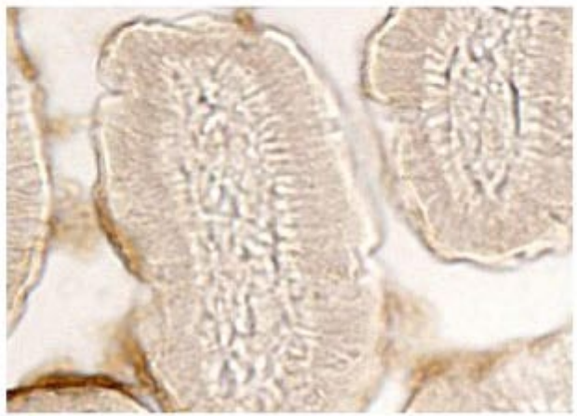
Period 01.01.2001 - 31.12.2003

Elucidating the Function of HNF4γ

HNF4γ is a member of the nuclear receptor family the function of which is unknown since a mutation of this gene has thus far not been generated. In previous experiments we have observed expression in intestine and pancreas and low-level expression in liver and kidney. In the intestine HNF4γ is expressed in the villi of the intestinal epithelium. To learn more about the function of HNF4γ we have employed RNAi for inactivation in the mouse using a lentiviral vector system. We generated mice expressing different shRNA against HNF4γ, analyzed the integration of the vectors, studied the expression of EGFP driven by the CMV promoter contained within the viral genome, as well as the expression of siRNA which is driven by the U6 promoter. Founder mice display a high mosaicism in the expression of siRNA. Thus it was necessary to study F1 mice for evaluation of this strategy. A rather low efficiency of transgenesis for F1 mice was found. We could observe some mutants which show a knockdown of HNF4γ expression in the islands of the pancreas as well as in the intestine.

When verified by realtime PCR we could demonstrate a 80% knock-down of HNF4γ mRNA expression in the pancreas in particular in β-cells of the pancreatic islands. No gross phenotypic alterations were found. Thus, we conclude that this methodology will be useful, but that the level of expression of siRNA may have to be raised in order to get stronger consequences of the mutation. With these mice it will be of interest to follow the capacity of polyunsaturated fatty acids (PUFA) of fish oils to suppress the transcriptional activity of HNF4γ, as observed in the laboratory of Dr. Bar-Tana, and compare the functional consequences in wild-type and mutant mice. We may anticipate functional consequences as predicted by the Israeli partner.

Knockdown of HNFγ activity in the intestine.
Immunohistochemical analysis with a specific antiserum to HNF4γ reveals disappearance of the antigen in the villi of the intestine.



A biochemical and molecular genetic approach to study the role of hepatocyte nuclear factor 4 (HNF4) and suppression of tumor development by fatty acids

J. Bar-Tana, R. Hertz, Hebrew University, Jerusalem
G. Schütz, DKFZ Heidelberg

Period 01.01.2001 - 31.12.2003

Integrin Signalling in Men and Mice

Signaling at the Footsteps of Epidermal Keratinocytes and Skin Cancer Cells

This cooperation has a very long history. Our friendship started when Tammy and I met in the tissue culture facility of Stuart Yuspa's division at the National Cancer Institute, Bethesda: Tammy, being a young enthusiastic researcher falling in love with culture of mouse epidermal keratinocytes and myself, a guest scientist adapting our human epidermal HaCaT cells (Norbert Fusenig's laboratory) to the NIH-microenvironment. Attending often the same meetings we shared our findings, her working with tumorigenic mouse, me with human cells. Particularly striking for both systems was that integrin α6β4, a cell surface molecule crucial for epidermal attachment to the dermal matrix in skin, became widely dislocated in developing experimental tumors. Getting deeply into molecular mechanisms, Tammy's group discovered that members of the protein kinase C family, PKCα and -δ regulate α6β4 functions. Thus, enjoying the social environment of New England conferences, we decided definitely to apply for our cooperation project on integrin signaling, the contribution of PKC governed pathways, and consequences on normal and pathological processes in the epidermis. Dealing with men and mice, we confirmed that posttranslational modification is a major mechanism in integrin regulation, also in human cells, controlling activation and degradation. First, we identified specific integrin subunits (α3, α6 and β1, β4) and PKC isoforms linked to integrin-PKC mediated inside-out signaling in skin. Strong PKC effects were found on expression, phosphorylation, and localization of α6β4, responsible for stable adhesion, while the pro-migratory α3β1 was only mildly affected. Next, we identified specific PKC isoforms (PKCα, -δ, and -ζ) linked to integrin signaling. Applying integrin-harboring adenoviral vectors revealed a positive response by PKCα/α6β4-complexes, favoring cell adhesion, and the opposite by PKCδ/α6β4, promoting migration. The relevance of the mouse data was underlined by using human keratinocytes. Investigating the PKC-mediated α6β4 expression and function in tumor progression in vitro, the expanding α6β4 patterns (in parallel to malignant conversion) were linked to decreased PKCδ and increased PKCα. This correlates to the α6β4 increase during cancer progression and reduced differentiation being a hallmark of late stage carcinomas. However, differences between mouse and human keratinocytes were found by integrin overexpression utilizing recombinant adenoviruses. Mouse cells high in α6 upregulated the respective β4, but instead, in normal human and HaCaT cultures α6-infection induced cell death. There was no rescue by other means, such as organotypic coculture with skin fibroblasts. This implies a signaling default due to α6/β4-dysbalance. We confirmed this by infecting HaCaT cells with retroviral (mouse) α6- or β4-vectors. High β4-levels were found in stable β4-infected cells, appearing normal, while after α6-infection clonal selection took much longer due to massive cell loss. Further, although mouse α6 was clearly detectable, there was no real increase of total α6, being strictly co-localized with β4. Finally, our results on PKCs were confirmed in transgenic mice, null to PKCα or -δ, both of which being defective in α6β4-regulation. In summary, our studies illustrate interactions of transduction elements converting chemical into physical signals or vice versa in normal and diseased skin.

Dirk Breitkreutz and Tamar Tennenbaum

While I was too busy to see her during my stay in Tel Aviv in March 2005, Tammy forgave me in June at a meeting on neutral grounds, in Italy. So, our great relations are robust to irritations.

The functional relevance of alterations in integrin α6β4 and protein kinase C regulation in human and mouse skin carcinogenesis

T. Tennenbaum, Bar-Ilan University, Ramat-Gan
D. Breitkreutz, DKFZ Heidelberg

Period 01.01.2001 - 31.12.2003

Resensitizing Tumors to Programmed Cell Death

Tumor Counterattack

Gideon Berke and Peter Krammer collaborated on the topic of ‚tumor counterattack' because both scientists are specialists in the complementary fields of killer cells (G. Berke) and apoptosis (P. Krammer).

Research in tumor immunology has provided a wealth of information about the interactions between tumors and the immune system. Many of these interactions are now not only known on a cellular, but also on a molecular level. Despite this knowledge, cancer immunotherapy still is not an established treatment in the clinic. Many approaches may fail because tumors use multiple mechanisms to become resistant to apoptosis or to counterattack the immune system. These mechanisms render tumor cells insensitive to the effector mechanisms of the immune system, yet the significance for immune escape has only been shown in few studies. It was the aim of our research in this area to understand these events further and to use this insight to resensitize tumor cells to apoptosis. Recently, it has been shown that low doses of chemotherapy or irradiation sensitized resistant cells to TRAIL-induced apoptosis *in vitro* and *in vivo*. Therefore, these treatments might enhance the susceptibility of a tumor to immune attack. A future therapeutic strategy may also involve down-regulation of anti-apoptotic molecules such as FLIP or Bcl-2 by antisense oligonucleotides or dsRNA interference. However, a macroscopic tumor is heterogeneous, and different cells within the tumor may also use different immune escape mechanisms including apoptosis resistance, impaired antigen presentation, secretion of immunosuppressive factors, and other strategies. Moreover, multiple mechanisms may develop in a single tumor cell. Therefore, it is questionale whether a single, predominant immune-escape mechanism can be identified in a tumor and whether therapeutic targeting of one mechanism alone is promising.

In our studies we found that tumor cells can express killer ligands on the cell surface that kill attacking T lymphocytes. Such *in vitro* findings still need to be further verified *in vivo*, in animals or in patients. Deeper insight into the molecular mechanisms underlying tumor immune escape may finally lead to novel therapeutic approaches that will be used for the benefit of cancer patients.

The CD95 (APO-1/Fas) death system in tumor progression

G. Berke, Weizmann Institute Rehovot
P. Krammer, DKFZ Heidelberg

Period 01.07.2002 – 30.06.2005

Insulin's Role Beyond Sugar Metabolism

Insulin Signaling in Skin – Impact on Epidermis

One hallmark of this project was the intense personal exchange. At DKFZ we could host not only the head of our partner laboratory Efrat Wertheimer, but also the Ph.D. students Marianna and Jenny for several weeks. In return, my student Sonja and I had the pleasure to meet the whole laboratory in Tel Aviv (attending a status meeting) and to share a wonderful authentic dinner in Jerusalem; Sonja presented a poster there together with Jenny in December 2005.

Committed to skin, getting involved in insulin signaling was kind of a challenge, whereas Effy had focused on glucose transport and metabolism in muscle. After her move towards skin, epidermis became our common base. A rationale of our project was the rising incidence of diabetes, associated with skin pathologies and a higher risk for skin cancer. Effy's group had demonstrated insulin responsiveness in mouse skin, compatible with our findings in human epidermal cell culture. Thus, the concept was to elucidate insulin and related signaling pathways and reversely to redirect responses by rigid impact on involved molecular elements in mouse and human cells. Corresponding to mouse, insulin-signaling elements and their interactions were analyzed in the human keratinocyte line HaCaT and in a malignant (ras-transfected) variant. Levels were comparable for insulin receptor (IR), the related insulin-like growth factor1 receptor (IGF1R), insulin receptor substrate-1 (IRS1), interacting protein kinase C isoforms (PKCα, -δ), and typical integrins, representing cell-matrix receptors. In HaCaT cells, insulin enhanced binding of PKCδ and specific membrane molecules, inducing phosphorylation, whereas binding of PKCα and integrin α6β4 was reduced. Analyzing lipid rafts (multifunctional cell membrane domains) it was found that insulin causes a shift of IR/caveolin adducts to higher complexes seen on density gradients. Insulin and IGF1 effects partially overlapped in mouse skin and in three-dimensional (3D) epidermal/fibroblast cocultures with mouse or human cells. Both hormones generally promoted basal cell functions (basement membrane, proliferation), but the late differentiation markers were diminished, by insulin in mouse also early markers. To abolish insulin signaling 'skin-specific IR knockout' (SIRKO) mice were raised, generating also 3D-cocultures. As a human pendant, IR was suppressed by RNA interference (siRNA) in HaCaT cells; this knock-down (kd) approach was applied for IGF1R, too. In transient assays suppression by siRNAs could exceed 95%. Correlating to receptor levels, growth was largely reduced, in particular suppressing IGF1R. Conversely, differentiation was enhanced, but in addition IGF1R-kd induced vast cell apoptosis and detachment. A permanent IR-kd was installed in HaCaT by DNA-vectors, producing siRNA with 80-90% suppression in some clones. While levels of α6, β4, and PKCδ diverged, PKCα was reduced like IR. Those cells showed enhanced migration, especially under IGF1. In 3D-coculture they formed stratified, but mostly thinner epithelia (impaired growth) similar to SIRKO-cells. Cells high in α6β4 were partly invading matrix, together with reduction of polarity and epidermal markers (e.g. keratins) resembling tumor grafts. In contrast, induced IGF1R knockout (adenoviral cre-vector) in 3D-cocultures of transgenic murine cells (recombinant targeting, floxed IGF1R) revealed growth reduction and premature terminal differentiation, compromising long-term survival.

Taken together, our combined approaches, expertise, and methodology – inspired by personal interactions – should provide fruitful seed and soil for further collaborative efforts.

Functional significance of insulin signaling in skin and skin tumorigenesis

E. Wertheimer, Tel Aviv University
D. Breitkreutz, DKFZ Heidelberg

Period 01.07.2002 – 30.06.2005

Sonja, Dirk and Effy in front of the Western Wall in Jerusalem

Cancer - A Consequence of Fragile Chromosomes?

The Division of Tumour Genetics – former Cytogenetics – enjoys a long tradition in collaborating with Israeli scientists within the DKFZ-MOST framework. In historical order, colleagues have included top Israeli scientists Yossi Shiloh, Dani Canaani, Moshe Oren, Adi Schimke, and currently Batsheva Kerem. Among these, our cooperation with Moseh Oren has been elected a "Highlight Project". Our common interest all along has been directed at defining molecular pathways of genetic instability in cancer development. Early collaborations had dealt with the amplification of the *MYCN* gene in neuroblastomas, which had been the first human genetic tumour marker identified by array technology and at the same time the first prognostic genetic tumour marker alluded to as the "clinical debut of oncogenes". The current collaboration emphasizes genomic rearrangements, including DNA amplification, by analyzing gene damage consequent to the activation of Common Fragile Sites. For this, our Israeli partner Batsheva Kerem is one of the international pioneers.

Central to our projects is the idea that genetic instability is a hallmark of at least a majority of cancer cells. While the normal cell has evolved specific molecular mechanisms involving both repair pathways to ensure DNA replication fidelity and checkpoints to maintain chromosomal stability during cellular multiplication, most cancer cells to a large extent have lost the ability to maintain genomic integrity. The consequence is often widespread genomic instability, which in most advanced cancers can be demonstrated as chromosomal rearrangements, such as deletion, translocation and amplification. Independent genomic damage at different genetic loci among members of tumour cells in the same affected patient will result in the generation of genetic tumour cell heterogeneity.

Evidence is accumulating that one of the molecular pathways for chromosomal rearrangements starts from „Fragile Sites". These are non-random, predetermined chromosomal breakage regions of the genome present in all human individuals, and also certain animal species, that can be activated experimentally by a number of exogenous challenges. The inappropriate repair of such breaks can result in genomic damage. In recent years, there has been exciting progress in this field, and molecular pathways have been described that identify the activation of Fragile Sites as one of the possible initiating events in the generation of chromosomal damage related to tumour progression and to resistance against therapeutic drugs. Additionally, evidence is accumulating that Fragile Sites may be related to non-malignant types of chronic human diseases (also featured in DKFZ journal „einblick", November 2005).

International activities in Fragile Site research are coordinated under the umbrella of the *FRAGILOME* acronym, supported by the European Science Foundation (ESF) scheme within the Framework of COST B19 "Molecular Cytogenetics of Solid Tumours". This activity aims at determining the full repertoire of Fragile Sites present in the human genome, identifying the genetic information at risk for damage upon expression of the Fragile Sites, and finding out the types of cancerous and non-cancerous human diseases associated with genomic damage consequent to the expression of Fragile Sites. A recent presentation platform has been the International *FRAGILOME* meeting in Heidelberg during February 17-19, 2005 (http://intl.elsevierhealth.com/journals/cale/). The lecture by Batsheva Kerem has been a particular highlight.

FRAGILOME research within the Division of Tumour Genetics also enjoys a fully international touch with young investigators from Austria, Germany, Italy, Poland, and Russia engaged in a fruitful, productive, and harmonious interaction. Taken together, our combined approaches, expertise, and methodology - inspired by personal interactions - should provide fruitful seed and soil for further collaborative efforts.

The international FRAGILOME *group at the Division of Tumour Genetics. From left to right: Evgeny Sagulenko (Russia), Fabiola Panucci (Italy), Anne Fechter (Germany), Larissa Savelyeva (Head of* FRAGILOME *Group; Russia), Elisabeth Kühnel (Austria), Malgorzata Sawinska (Poland), Jens Schmitt (Germany)*

Chromosomal fragile sites and cancer
B. Kerem, Hebrew University, Jerusalem
M. Schwab, DKFZ Heidelberg
Period 01.01.2004 – 31.12.2006

DKFZ-MOST Cooperation Program in Cancer Research
II. History

2003 25th Anniversary Symposium in Berlin Magnus-Haus
Honorary lecture by Aaron Ciechanover,
Nobel Prize winner in Chemistry in 2004

2001 New Intellectual Property Rights

1999 Brochure „Cooperation and Friendship“
with comprehensive list of publications

1997 International Reviewing of the Program
by Professors Kleihues, Fleckenstein, Sachs;
Results → „excellent“

1997 Meyenburg Lecture by Professor Dr. Michael Schlesinger,
Israeli Member of the Program Committe

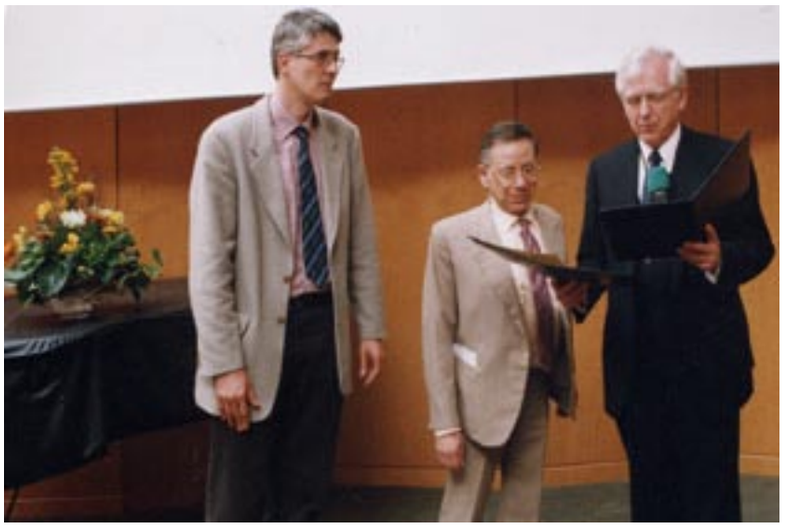
1997 20th Anniversary at DKFZ,
honouring of 7 highlight projects

1986 10th Anniversary in Jerusalem (Hebrew-University)

1976 Foundation of the Cooperation, Agreement between National
Council of Research and Development and DKFZ

DKFZ-MOST Cooperation Program in Cancer Research
Symposium 20th Anniversary, March 1997, at DKFZ

Professor Dr. Michael Schlesinger, Member of the Israeli Program Committee since 1987, was honoured by the 1st Meyenburg Lecture of DKFZ. He delivered the lecture in September 1997.



Professor Dr. Martin Löchelt and Professor Dr. Mordechai Aboud receive a certificate for their highlight project entitled „Tumorigenic cooperation between human retroviruses, oncogenes and other carcinogens“

DKFZ-MOST Cooperation Program in Cancer Research

Symposium 25th Anniversary, March 2003, in Berlin, Magnus-Haus

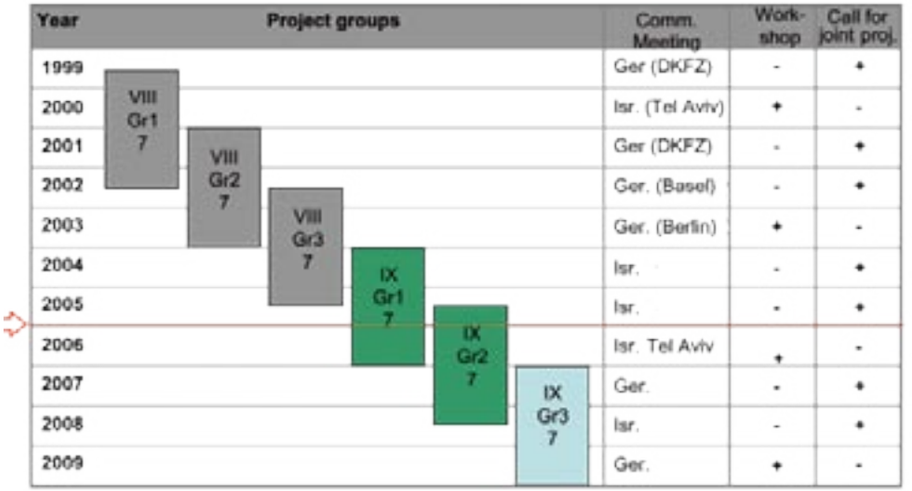
The auditorium, first row left Ambassador Shimon Stein, next Staatssekretär Dr. Uwe Thomas who had both delivered greeting addresses at the beginning of the symposium

Professor Dr. Harald zur Hausen honours Dr. Yair Degani (former MOST Coordinator) by the Silver needle of the DKFZ. Left Professor Dr. Erich Hecker (former DKFZ Coordinator), right Professor Dr. Dr. Wolfhard Semmler (present DKFZ Coordinator)

Professor Dr. Erich Hecker receives a present by Professor Aaron Ciechanover, Representative Technion Haifa and key note lecturer at this symposium

DKFZ-MOST Cooperation Program in Cancer Research
III. Appendix

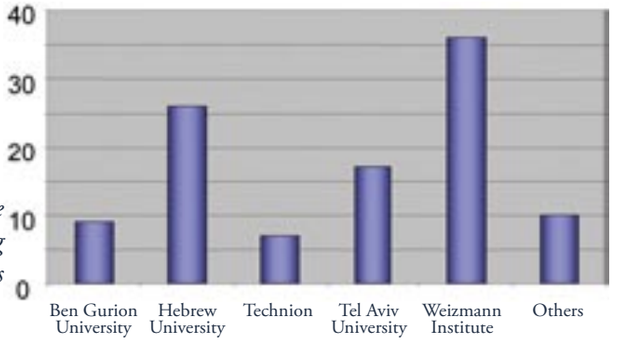
1. Masterplan 1999 - 2009



Project status for the years 1999 until 2009: always two groups of cooperational projects are working and financed in parallel (concluded ■; ongoing ■; planned ■)

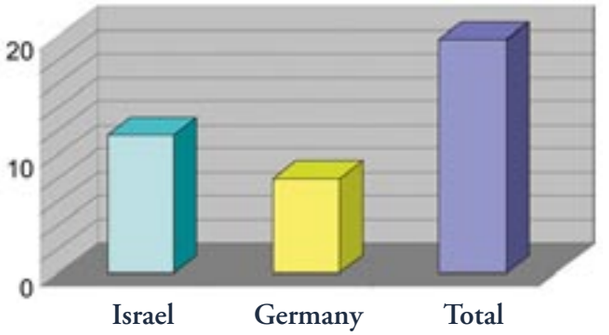
2. Projects of Israeli Research Institutes

Distribution of the research projects among the Israeli institutions



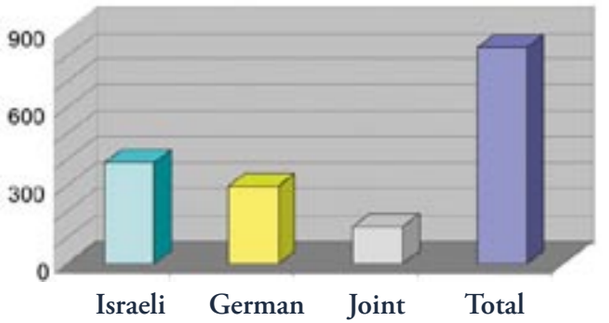
3. Finances from the period of 1976 to 2004

Total finances from the period of 1976 to 2004: 19.7 Million €uro



4. Publications from the period of 1976 to 2004

The scientific output of the co-operations amounts over 800 publications in well-renowned journals



DKFZ-MOST Cooperation Program in Cancer Research

List of Workshops/Status Seminars

1st Workshop 1979

Deutsches Krebsforschungszentrum (DKFZ), Heidelberg, Germany

2nd Workshop 1982

Kibbutz Kiryat-Anavim, near Jerusalem, Israel

3rd Workshop 1985

Hotel Salina, Breiten, Switzerland

4th Workshop 1988

Dan Accadia Hotel, Herzlia, near Tel Aviv, Israel

5th Workshop 1991

DKFZ Heidelberg, Germany

6th Workshop 1994

Moriah Plaza Hotel, Tel Aviv, Israel

7th Workshop 1997 - together with 20th Anniversary Symposium

DKFZ, Heidelberg, Germany

8th Workshop 2000

University of Tel Aviv, Israel

9th Workshop 2003 - together with 25th Anniversary Symposium

Magnus-Haus Deutsche Physikalische Gesellschaft, Berlin, Germany

10th Workshop 2006 - together with 30th Anniversary Symposium

Sheraton-Moriah Hotel, Tel Aviv, Israel

Weizmann Institute of Science, Rehovot, Israel

DKFZ-MOST Cooperation Program in Cancer Research
List of Projects Ca001 - Ca120

Project phase I – 01.01.1976 - 31.12.1979

001 *Integration of SV40 into the cellular genome*

E. Winocour, Weizmann Institute of Science
G. Sauer, DKFZ

002 *Membrane organisation in leukemic cells – kinetics of formation and heterogeneity of surface membrane components and mosaics and its interference with membranotropic drugs*

L. Sachs, Weizmann Institute of Science
W. Franke, DKFZ

007 *Regulation of synthesis of HnRNA in epidermis cells of insects and its posttranscriptional modification*

E. Shaaya, Hebrew University
E. Sekeris, DKFZ

Project phase II – 01.01.1977 - 31.12.1980

003 *Analysis of lymphocyte subpopulations with a combination of physical and serological techniques*

M. Schlesinger, Hebrew University
W. Droege, DKFZ

004 *Control mechanisms of immunoglobulin synthesis in myeloma cells*

R. Laskov, Hebrew University
K. Eichmann, DKFZ

005 *Cell surface shedding in normal and neoplastic cells*

F. Doljanski, Hebrew University
V. Kinzel, DKFZ

Project phase III, group 1 – 01.07.1979 - 30.06.1982

008 *Differentiation of normal and malignant T and B lymphocytes*

J. Haimovich, Tel Aviv University
P. Krammer, DKFZ

009 *Synergistic carcinogenic effects of viral and chemical agents and DNA mutagenesis in primates*

S. Lavi, W. Winocour, Weizmann Institute of Science
G. Sauer, DKFZ

010 *Systemic and in-situ tumoral immunity in rats inoculated with herpes-simplex virus (HSV) transformed cells and bearing metastasising tumors*

J. Witz, Tel Aviv University
K. Munk, DKFZ

011 *Mechanism of immunosuppression in cancer patients and experimental models. The role of adjuvant radio-chemo- and immunotherapy*

T. Mekori, E. Robinson, Technion
H. Kirchner, E. Storch, DKFZ

012 *Identification and biological activity of antigens in immune complexes of patients with breast cancer*

D. Sulitzeanu, Hadassah Med. School
M. Zöller, S. Matzku, DKFZ

013 *Specific adoptive immunotherapy of human and experimental tumors by lymphocytes sensitized in vitro against autologous tumor cells*

J. Treves, S. Biran, Hadassah University Hospital
W. Dröge / V. Schirrmacher, DKFZ

Project phase III, group 2 – 01.10.1979 - 30.09.1982

014 *Macrophage activation induction and effects on cell cooperation*

E. Pick, Tel Aviv University
D. Gemsa, H. Kirchner, DKFZ

015 *Expression of immunoglobin variable region determinants on functionally defined T lymphocyte populations*

D. Givol, P. Lonai, Weizmann Institute of Science
K. Eichmann, DKFZ

016 *A study of the mechanism of environmental carcinogenesis*

R. Ben-Ishai, Technion
H. W. Thielmann, DKFZ

Projects phase III, group 3 – 01.07.1981 - 30.06.1984

017 *Biochemical dissection of early promotion specific and pleiotropic effects evoked by phorbol ester tumor promoters and related compounds*

R. Simantov, Weizmann Institute of Science
F. Marks, DKFZ

018 *The immunobiology of tumor metastases*

S. Segal, E. Gorelik, Ben-Gurion University
G. Haemmerling / V. Schirrmacher, DKFZ

Project phase IV, group 1 – 01.07.1982 - 30.06.1985

019 *Virus-mediated genetic rearrangements*

E. Canaani, Weizmann Institute of Science
T. Graf, DKFZ

020 *Nucleic acid binding activities and nucleolytic activities associated to the nuclear matrix in mammalian cells*

M. Herzberg, Tel Aviv University
D. Werner, K. Munk, DKFZ

021 *Alteration of growth regulation in chemical carcinogenesis*

J. Kapitulnik, R. Koren, Hebrew University
F. Kolar / N. Fusenig, DKFZ

Project phase IV, group 2 – 01.01.1983 - 31.12.1985

022 *Biochemical and immunochemical characterization of type-specific intermediate filaments and their attachment sites in normal and in transformed cells*

B. Geiger, Weizmann Institute of Science
W. Franke, DKFZ

023 *Cytostatic binding sites in normal and corresponding tumor cells*

U.Z. Linttauer, I. Ginzburg, Weizmann Institute of Science
H. Ponstingl, DKFZ

024 *Interaction of metastasizing and non-metastasizing tumors with cultured vascular endothelial cells and their underlying lamina*

I. Vlodavsky, Hadassah University Hospital
V. Schirrmacher, DKFZ

025 *Structure of cAMP-dependent kinases as bioregulatory enzymes*

S. Shaltiel, Weizmann Institute of Science
V. Kinzel, M. Gagelmann, DKFZ

Project phase IV, group 3 – 01.07.1984 - 30.06.1987

026 *Inhibition by interferon of herpes simplex virus or regulation of other viruses in murine cells*

A. Panet, Hebrew University
H. Kirchner, H. Jacobsen, DKFZ

027 *The molecular genetics of tumor growth*

M. Bar-Eli, Ben Gurion University
G. Haemmerling, DKFZ

028 *Lymphokine receptors on murine B- and T-cell tumors*

R. Kaempfer, Hebrew University
P. Krammer, DKFZ

029 *Escape mechanisms of metastatic tumor variants*

A. Raz, A. Ben-Ze'ev, Weizmann Institute of Science
M. Zoeller, DKFZ

Project phase V, group 1– 01.01.1986 - 31.12.1988

030 *P53 expression in tumor cells of different metastatic capacity*

V. Rotter, Weizmann Institute of Science
V. Schirrmacher, DKFZ

031 *Detection and characterization of human papilloma viruses in genital lesions from Israelian patients*

S. Mitrani-Rosenbaum, Hebrew University
L. Gissmann, DKFZ

032 *The role of DNA-amplification in tumor initiation*

S. Lavi, Tel Aviv University
J. Schlehofer, DKFZ

033 *The role of plasma membrane physical organization in control of growth and differentiation of human epidermal cells*

Y. Milner, Hebrew University
M. Hergenhahn, DKFZ

034 *The role of polypeptide growth factors in multistage tumorigenesis*

J. Schlessinger, Weizmann Institute of Science
V. Kinzel, F. Marks, DKFZ

035 *Carcinogen induced replication and recombination of polyoma and lymphotropic papovavirus DNA*

H. Manor, Technion
M. Pawlita, DKFZ

Project phase V, group 2 – 01.07.1987 - 30.06.1990

036 *Intermediate filaments in germ cell tumors*

B. Czernobilsky, Kaplan Hospital
W. Franke, DKFZ

037 *Role of cell surface-mediated utilization of extracellular nucleotides in normal and transformed cells*

I. Friedberg, Tel Aviv University
D. Kübler, W. Pyerin, DKFZ

038 *Induction of cytolytic lymphocytes by cytokines*

Dr. Y. Kaufmann, Chaim Sheba Medical Center
W. Falk, P. Krammer, DKFZ

039 *Agents controlling the growth and differentiation of primitive blood lymhomyeloid/erythroid stem cells*

M. Revel, Weizmann Institute of Science
R. Zawatzky, H. Kirchner, DKFZ

Project phase V, group 3 – 01.01.1989 - 31.12.1991

040 *Biochemical predictors of 20 years cancer incidence in the Israeli Civil Servant Cohort*

J. Kark, Hebrew University
J. Wahrendorf, DKFZ

041 *Mechanisms controlling the response to tumor necrosis factor*

D. Wallach, Weizmann Institute of Science
D. Maennel, DKFZ, H. Holtmann, University Hannover

042 *Immunotherapy by tumor infiltration lymphocytes (TIL) activated by IL-2: The development of large granular cytolytic T lymphocytes (LGCTL) and the function of lytic granules and perforins(s) in inducing tumor regression*

G. Berke, Weizmann Institute of Science
W. Droege, DKFZ

043 *Application of human cytokine and effector cells for immunotherapy of human tumors in nude mice*

E. Kedar, Hebrew University
V. Schirrmacher, DKFZ

044 *Cytokine secretion of tumor cells influence on tumor initiation, progression and interaction with the immune system*

R. N. Apte, Ben Gurion University
M. Zoeller, DKFZ

045 *Dietary factors in the recurrence and progression of colorectal adenomas; A calcium intervention study*

P. Rozen, Ichilov Hospital
H. Boeing, DKFZ

Project phase VI, group 1 – 01.07.1990 - 30.06.1993

046 *Regulation of synthesis of intermediate filament and desmosomal proteins in attached and unattached states of normal and transformed cells*

A. Ben-Ze'ev, Weizmann Institute of Science
J. Kartenbeck, W. Franke, DKFZ

047 *Amplification in human solid tumors: search for new oncogenes*

Y. Shiloh, Tel Aviv University
A. Weith, M. Schwab, DKFZ

048 *Involvement of the NS genes in the antitumor activity of parvoviruses*

J. Tal, Ben Gurion University
J. Schlehofer, DKFZ

049 *Structure-function relationships in adhering cell junctions of normal and transformed cells*

B. Geiger, Weizmann Institute of Science
W. Franke, DKFZ

Project phase VI, group 2 – 01.01.1992 - 31.12.1994

050 *Tumorigenic cooperation between human retroviruses, oncogenes and other carcinogens*

M. Aboud, Ben Gurion University
R. Flügel, M. Löchelt, DKFZ

051 *Analysis of tumor suppressor genes in human cancers*

M. Oren, Weizmann Institute of Science
M. Schwab, DKFZ

052 *Development of NMR and mass spectroscopic techniques and their application in the investigation of fatty acid and phospholipid metabolism and alterations involved in cellular transduction and malignant growth*

H. Degani, Y. Salomon, Weizmann Institute of Science
W. Lehmann, W.E. Hull, DKFZ

053 *Transforming growth factor-beta in epithelial growth control, differentiation and neoplasia*

S.A. Lamprecht, Ben Gurion University
G. Fürstenberger, F. Marks, DKFZ

054 *Role of phospholipase C and D in cell signaling and growth control*

M. Liscovitch, Weizmann Institute of Science
V. Kinzel, DKFZ

055 *Cell signaling and growth control induced by amphipathic carboxylates – an unifying theory*

J. Bar-Tana, Hebrew University
D. Keppler, DKFZ

Project phase VI, group 3 – 01.07.1993 - 30.06.1996

056 *Arrest of cell division in tumor cells by inducing expression of control proteins: (A) Cytoskeletal Tau MAP (Israel), (B) Mitotic Control Proteins (Germany)*

I. Ginzburg, Weizmann Institute of Science
H. Ponstingl, DKFZ

057 *Growth factor regulated interaction between leukemias/lymphomas and endothelium*

G. Neufeld, Technion
R. Schwartz-Albiez (div. V. Schirrmacher), DKFZ

058 *Regulation of proteases and their respective inhibitors mediating cell invasiveness during angiogenesis and metastasis*

E. Keshet, Hebrew University
E. Spiess (div. W. Franke), DKFZ

059 *Negative regulating growth factors and the significance of their abrogation in carcinogenesis*

A. Kimchi, Weizmann Institute of Science
N. E. Fusenig, DKFZ

060 *Onco suppression by adeno-associated viruses*

S. Lavi, Tel Aviv University + R. Heilbronn, Max-Planck-Institut für Biochemie, Martinsried / J. Kleinschmidt, DKFZ

061 *The involvement of tumor suppressor p53 in differentiation*

V. Rotter, Weizmann Institute of Science
K.H. Richter (div. F. Marks), DKFZ

062 *Signaling pathways of Drosophila receptors and tumor suppressor gene products*

B. Shilo, Weizmann Institute of Science
B. Mechler, DKFZ

Project phase VII, group 1 – 01.01.1995 - 31.12.1997

063 *Phosphorylation of proteins encoded by oncogenes and tumor suppressor genes as a determinant for protein association and tumorigenesis*

D. Canaani, Tel Aviv University
M. Schwab, DKFZ

064 *The influence of TAP peptide transporters on tumorgenisity*

S. Segal, Ben Gurion University
F. Momburg (div. G. Haemmerling), DKFZ

065 *Regulation of gene expression in tumor growth: over expression of phospholipase A2 and prostaglandin H synthase isoenzymes as potential markers for epithelial tumors*

U. Zor, Weizmann Institute of Science
G. Fuerstenberger (div. F. Marks), DKFZ

066 *Induction of immune response against T cell lymphomas by IL-1alpha and anti-CD44v monoclonal antibodies*

R. Apte, Ben Gurion University
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067 *Induction on tumor cell apoptosis by killer cells*

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V. Schirrmacher, DKFZ

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071 *Molecular basis of the resistance of tumor cells to complement-mediated lysis*

Z. Fishelson, Tel Aviv University
M. Kirschfink, University of Heidelberg

072 *Functional interaction of pX of HBV with the tumor suppressor p53*

Y. Shaul, Weizmann Institute of Science
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073 *Human papillomavirus (HPV) transformation: The role of HPV16 E6 in the induction of resistance to serum/Ca2+ mediated differentiation*

L. Sherman, Sackler School of Medicine
M. Dürst (div. A. Alonso), DKFZ

074 *Redirecting effector lymphocytes to Hodgkin's disease/lymphoma using chimeric receptors with antibody specificity*

Z. Eshhar, Weizmann Institute of Science
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075 *Possible role of AML2 and other genes on distal chromosome 1p for human cancers*

Y. Groner, Weizmann Institute of Science
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076 *Imprinted genes in human cancer, biology, diagnosis and therapy*

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077 *The importance of cyclin D1, RB, K-ras and cyclin-like CENP-C in cell cycle control and progression*

N. Arber, Tel Aviv University
W. Pyerin, DKFZ

078 *The role of avb3 integrin and protease activated receptor in tumor metastasis: involvement of thrombin-receptor (ThR) and L1 adhesion molecule*

R. Bar-Shavit, Hadassah Med. School – Hospital
P. Altevogt (div. V. Schirrmacher), DKFZ

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A. Ben Ze'ev, Weizmann Institute of Science
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M. Scheffner (div. E.M. de Villiers), DKFZ

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K.-M. Debatin, DKFZ

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A. Kimchi, Weizmann Institute of Science
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088 *Development and evaluation of non-viral antisense oligonucleotide and gene controlled delivery systems for the treatment of mammary carcinoma and bone osteolysis*

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089 *Role of PDGF and VEGF in blood vessel formation, maturation and regression: New targets for tumor therapy*

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090 *Novel inhibitors of tumor metastasis and angiogenesis*

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091 *Sensitization of human tumor cells to complement-mediated lysis*

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B. Fehse, A.R. Zander, University Hospital Hamburg-Eppendorf

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M. Liscovitch, Weizmann Institute of Science
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