Krebsforschung und Kooperation

Cancer Research and Cooperation

Deutsches
Krebsforschungszentrum
Heidelberg

State of Israel
Ministry of Science
Jerusalem

Titelbild:
Frisch und früchtereich präsentiert sich die
Deutsch-Israelische Kooperation in der
Krebsforschung im dritten Jahrzehnt ihres
Bestehens - wie der abgebildete Apfelbaum,
den Kinder mit Kartoffelstempeln geschaffen haben

Cover Picture:
The German-Israeli Cooperation in Cancer Research, now
entering its third decade, is vigorous and fruitful like the
fruit-bearing apple tree in the illustration, which was
made by children using the technique of potato prints

Krebsforschung und Kooperation

Deutsch-Israelische Zusammenarbeit in der Krebsforschung - Die ersten 20 Jahre

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German-Israeli Cooperation in Cancer Research - The First 20 Years

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Greeting

Scientific and technological cooperation at an international level today is more important than ever for preserving or achieving peace, for improving people's lives and for advancing sustainable development.The cooperation between the Federal Republic of Germany and Israel in basic and applied research, which has existed for around 40 years, is a particularly important aspect of Germany's bilateral relations. The Federal Government supports and provides funding for this cooperation.

An example is the cooperation research program between the Deutsches Krebsforschungszentrum (DKFZ) and the Israeli Ministry of Science (MOS). The Federal Government has been providing the DKFZ in Heidelberg with around DM 1 million per year since 1976, and has funded a total of over 80 joint projects. In the first twenty years of the cooperation 61 joint projects have been concluded successfully. The work has led to globally-acclaimed publications, indicative of the scientific quality of the research results. Particularly notable progress has been made in the study of the molecular genetic basis of carcinogenesis. Important insights have also been gained into the interaction of cancer cells with their surrounding cells, and their mobility.

I am certain that these joint projects will continue to produce excellent results important not only for basic research but also for transfer into clinical practice. I believe that the German-Israeli scientific cooperation, which is characterized by a high standard of specialist knowledge, will continue to develop successfully in the coming years.

As a result of the cooperation over many years, a network has developed which is supported by numerous personal contacts beyond the specialist level. These friendly relations help to increase mutual understanding and to break down divisions between the two cultures and nations. I believe that this is just as important and as desirable as the joint scientific successes.

Edelgard Bulmahn
Federal Minister of Education and Research (Germany)

Greeting

For 25 years, beginning in 1973, the science ministries of the State of Israel and the Federal Republic of Germany have administered an extensive, multi-field program of bilateral research cooperation. This publication marks the twentieth anniversary of ministry-sponsored cooperation in cancer research, one of the most outstanding disciplinary programs within the overall German-Israeli framework.

During the course of 20 years of cooperation in cancer research, the Ministry of Education and Research (BMBF) of the Federal Republic has provided over DM 16 million in grants to Israeli scientists taking part in more than 60 bilateral projects. Additional funding for German and Israeli researchers has been provided from its own budget by the German Cancer Research Center (DKFZ), which is responsible for implementation of the cancer program on behalf of BMBF. The Ministry of Science (MOS) is deeply grateful to its German partner institutions for the crucial financial support.

German-Israeli scientific cooperation has developed in the shadow and under the influence of the murderous events of the Holocaust. Nonetheless, it is an objectively observable fact that as time goes by the emphasis in our scientific relations moves more and more from one-sided support to a genuine and mutually beneficial partnership. Thus, while the historic roots of our cooperation must never be forgotten, I am confident that today the scientific achievements realized to the benefit of both sides fully justify the continuation and intensification of our joint endeavours on the basis of professional considerations alone.

The achievements of the DKFZ-MOS Cancer Research Program are an outstanding example of the mutual scientific benefits which German-Israeli cooperation can bring. Over 500 published articles based on DKFZ-MOS projects, including about 100 jointly authored Israeli-German papers, testify to the extremely high scientific level achieved by the scientists whose work has been supported by the Program. Important breakthroughs have been made in DKFZ-MOS research projects which will aid in the development of effective measures for the prevention and cure of cancer, thus contributing to the health and welfare of all mankind.

I salute the many talented scientists and administrators whose efforts have made this Program such a success. The Ministry of Science looks forward to equally productive and mutually beneficial results from the next two decades of German-Israeli cooperation in cancer research.

Silvan Shalom
Minister of Science (Israel)

Preface

In 1976 the Deutsches Krebsforschungszentrum (DKFZ) signed the agreement on cooperation in cancer research, at that time with the National Council for Research and Development (NCRD) in Israel. Over the last 20 years a most lively and scientifically successful cooperation program has developed out of this formal piece of paper. It is based on the enthusiastic personal involvement of all participants at the Deutsches Krebsforschungszentrum, in the Israeli research establishments concerned and in the Israeli Ministry of Science (MOS) of today which administers the cooperation program on Israeli side. The cooperation program is funded through the budget of the DKFZ, presently amounting to slightly over DM 1,2 million per year.

The cooperation program is carried out by means of joint scientific projects, consisting as a rule of one Israeli and one DKFZ subproject and lasting for three years. In occasional rare cases, upon invitation, a particularly successful cooperation project may be extended. The projects take life from the many personal contacts between the Israeli and German co-investigators involved. In this way an intensive transfer of scientific know-how is ensured lasting for the entire period of each project. The most important means of exchange of experience and knowledge is considered to be common bench work in the laboratory during mutual visits in Israel and in Germany. Furthermore, every three years a common workshop takes place, a so-called status seminar. On this occasion the results from ongoing projects are presented and discussed critically by the plenum of the members of the scientific program committee and the scientists of the projects involved. The seventh Workshop of the cooperation program took place on March 17-20, 1997 in Heidelberg combined with the twentieth Meeting of the Program Committee. In the frame of these activities the twentieth anniversary of the cooperation program was honoured in a Festive Anniversary Symposium held at the DKFZ.

Through the cooperation program the Deutsches Krebsforschungszentrum has gained important new insights in various different areas of cancer research, for example, the generation of cancer diseases, especially their molecular biological basis, cancer immunobiology, the roles of growth and transcription factors and of oncogenes and tumor suppressor genes. Important results have also been obtained on the interaction of cancer cells with their surrounding matrix and their motility. During the last few years, using molecular biologic techniques the cooperation program has contributed especially to investigations of cancerogenesis by chemical and viral risk factors. In this context, for the first time, the basic paradigm of ”somatic gene mutation as the cause of cancerogenesis” postulated by Karl Heinrich Bauer in 1928 was confirmed experimentally at the molecular level and extended in depth. The late Karl Heinrich Bauer, Chief Surgeon of the University of Heidelberg, was one of the principal promoters of the establishment of the Deutsches Krebsforschungszentrum in 1964 in Heidelberg. Out of the knowledge gained concerning cancerogenesis at the molecular level numerous new approaches for the prevention of cancer diseases as well as for cancer therapy are beginning to emerge.

The successes so far achieved by the cooperative program have demonstrated that joint research on the spot by talented workers of both nations, through mutual stimulation of ideas and through exchange of new technologies and recently developed scientific methods, permits the capabilities of the individual scientist to be extended efficiently and in friendly partnership. In this way high ranking goals in the prevention, diagnosis and therapy of one of the most awful diseases of mankind may be reached. In 1997 the basic success of the first 20 years of this cooperation program was revealed independently by an international scientific evaluation, recommending continuation and extension of the program. Shortly thereafter, the structure of the future cooperative program has begun to appear: presently 14 new common projects are already in progress with the last seven projects beginning their collaboration on January 1, 1998. The next series begins on July 1, 1999.

Professor Dr. Erich Hecker
Coordinator and Vice-chairman of the Scientific Program Committee

Professor Dr. Dr. h.c. mult. Harald zur Hausen
Chairman and Scientific Member of the Management Board of the Deutsches Krebsforschungszentrum

Dr. Josef Puchta
Administrative Member of the Management Board of the Deutsches Krebsforschungszentrum

Preface

Since its beginning in 1976, the DKFZ-MOS cooperative program in cancer research has continually gathered momentum and has become one of the most successful fields of German-Israeli cooperation in scientific research in terms of genuine and fruitful integration. In the twenty-year period marked by this Anniversary Brochure, 61 joint projects have been completed. In the years since then, a further 20 project proposals have been approved. Scientists from five Israeli institutions have taken part in the DKFZ-MOS program, from the Hebrew University of Jerusalem, the Weizmann Institute of Science, the Tel-Aviv University, the Ben-Gurion University and the Technion, as well as of some of their affiliated hospitals. The participating Israeli scientists have collaborated with German partners involved in virtually all the research areas covered by the work of the DKFZ.

The DKFZ-MOS program is one component in the overall BMBF-MOS program which encompasses eight major fields of research. Contacts within the BMBF-MOS framework, whose initial impetus came from the moral and social spheres, have proven themselves through the years to be highly productive from the scientific point of view, to the mutual benefit of both sides. The field of cancer research was and continues to be particularly appropriate as a meeting ground for Israeli and German scientists. In cancer research, a common dedication to the preservation and prolongation of life and the improvement of the quality of life find expression, above and beyond any direct concern for the economic return on investment in research and development activities.

As judged by external reviewers, including the international evaluation committee appointed by the partner organisations, which reported in 1997, the scientific quality of the projects carried out in the DKFZ-MOS program has risen steadily through the years. The state-of-the-art, international standard of the research sponsored is evidenced by numerous publications in prestigious professional journals. Many of these publications were jointly authored by Israeli and German partner investigators, as indicated in the bibliographic supplement to this Brochure. Remarkable achievements, discussed at length in the body of this booklet, have been made in a number of centrally important areas of cancer research.

As a small country which seeks to maintain top-level standards in scientific research, Israel views the promotion of international scientific cooperation as an essential element in its research and development policy. In keeping with this approach, the Ministry of Science operates an extensive international program, including bilateral activities with some 25 partner countries and membership or observer status in major international scientific organizations and programs.

The DKFZ-MOS program provides noteworthy confirmation of the correctness of the national and ministerial emphasis on international scientific ties. In the German-Israeli cooperation in cancer research, mutual stimulation based on exchange of new ideas, novel technologies and methodologies, together with the pooling of human and material resources, have enabled the partner researchers on both sides to realize more ambitious goals to their mutual benefit.

On the Israeli side, the program is widely acknowledged as a most important and unique tool for the promotion of advanced cancer research at an international scientific standard. On the German side, the program is recognized as an especially effective instrument for supplementing the DKFZ research program through multidisciplinary collaboration with competent partners abroad. It is our deep conviction that the achievements of the DKFZ-MOS program, and the new opportunities for yet greater advances in the future, justify the continuation and, indeed, the strengthening and expansion of the German-Israeli cooperation in cancer research. The Ministry of Science looks forward to working together with the DKFZ to serve the interests of scientists and citizens in both Germany and Israel and to bring improvements in health care to all mankind.

Dr. Yair Degani
MOS, Head, Life Sciences Division,
and Coordinator of the DKFZ-MOS Cooperation Program

Dr. Neal Sherman
MOS, Head, Division for International Scientific Relations

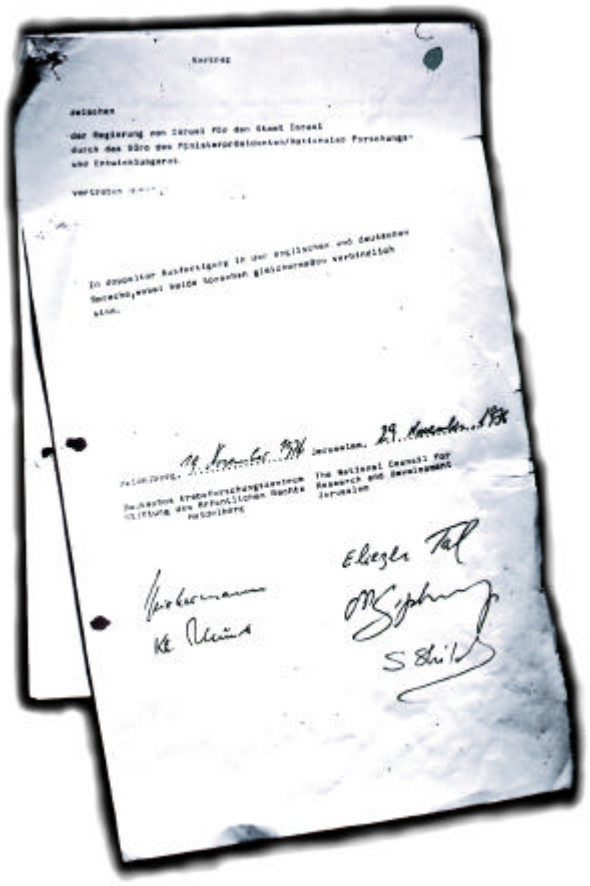
Summary

Close personal contact between scientists of both countries is a distinctive feature of the German-Israeli Cooperative Program in Cancer Research and the best guarantee of its success. In 1976 the Deutsches Krebsforschungszentrum (DKFZ) in Heidelberg and the Israeli National Council for Research and Development (NCRD) signed the agreement establishing this collaboration. It has funded 61 joint cancer research projects through 1996. In the years since then, a further 20 project proposals have been approved.

Each project is composed of complementary German-Israeli subprojects which (together) receive an annual allocation of about DM 130,000 for three years. Research visits between participating laboratories, joint workshops, annual subproject progress reports and joint project final reports are all standard procedure. A Program Committee composed of four Israeli and four German or European scientists annually selects six to eight new projects for funding and periodically reviews research progress.

The program is funded by the German Federal Ministry of Education and Research (BMBF), within the framework of its Research Program in Medicine: Subdivision Cancer. By the end of 1995, the BMBF had allocated more than DM 13 million to the DKFZ, which acts as the Ministry's authorized agent to transfer these funds to the administrators of the joint DKFZ-MOS Cooperative Program in Cancer Research. This cooperative program is part of a broader BMBF-MOS agreement which covers German-Israel cooperative research programs in seven areas of science and technology. Most Israeli partners of the program Cancer Research have come primarily from the Weizmann Institute (Rehovot), Hebrew University (Jerusalem) and Tel Aviv University. Researchers at Ben-Gurion University (Beersheva) and the Technion (Haifa) also participated. Most German-Israeli cancer projects represent basic biomedical research, whose research priorities conform to those of the DKFZ and MOS.

Scientifically, this program has been exceptionally successful. Over the past twenty years, the research findings of participating scientists have been published in close to 600 papers in internationally recognized scientific journals. Many such articles were published jointly by the German and Israeli collaborators. In 1997 an international commission for evaluation of the first twenty years recommended continuation of the program (see Appendix). The other great success of the German-Israeli Cooperative Program in Cancer Research has been in the many close friendships and bridges between the two nations it has initiated. While it cannot be expressed in numbers, this success is no less important.



"Between the Government of Israel ... and the Deutsches Krebsforschungszentrum ...": The official beginning of the Cooperation Program in November 1976

The Partner Organizations

The Deutsches Krebsforschungszentrum

Cancer research has developed rapidly over the last few years. Advances in molecular biology and gene technology open the possibilities of completely new therapeutic approaches to repairing the fatal genetic defects which cause tumorigenesis. The Deutsches Krebsforschungszentrum (DKFZ) was among the first to include such new approaches in its research program and it has actively contributed to their development.

The Deutsches Krebsforschungszentrum in Heidelberg, national research center for cancer research

The DKFZ was founded in 1964 as a public foundation. Since 1975 it has been one of Germany's Major Research Centers (Großforschungseinrichtung). It is financed, as are Germany's fifteen other Major Research Centers, by both the Federal Government (90 per cent) and by the State (Land) in which it is located (10 per cent). In the early 1990s, the Center's Management Board and Scientific Council, in collaboration with the DKFZ Board of Trustees, which supervises its affairs, modified the Center's rigid structure in order to promote more flexible research programs. Programs are now limited to six years duration, although these can be extended in the light of the scientific results obtained.

The DKFZ now has more than 45 scientific divisions, project and working groups, which are divided between eight multidisciplinary research priorities:

- Carcinogenesis and Differentiation
- Tumor Cell Regulation
- Cancer Risk Factors and Prevention
- Diagnostics and Experimental Therapy
- Radiological Diagnostics and Therapy
- Applied Tumor Virology
- Tumor Immunology
- Bioinformatics

The Center's Bioinformatics program was enlarged in 1996 to include genome research that is closely linked to the international efforts to systematically investigate man's genetic material.

The DKFZ regularly evaluates the quality and originality of its scientific work with the help of both internal experts and external scientists. It is the declared objective of the Center to make its research results available as quickly as possible, to enhance the prevention, diagnosis and therapy of malignant diseases. Thus the DKFZ is an active member of the Heidelberg/Mannheim Tumor Center, which is a close cooperating union of the DKFZ, the Faculty of Medicine of the University of Heidelberg, the University Hospitals and the Heidelberg Thorax Clinic. DKFZ experimental results can be put into clinical practice by joint teams of scientists and physicians cooperating within the framework of the DKFZ's five clinical cooperation units. The first two of these units, which are part of the Center both thematically and financially, were founded in 1993/94 in conjunction with the Pediatric University Clinic as well as the Medical and Outpatient Clinic of the University of Heidelberg in the fields of hematology and pediatric oncology, respectively. The clinical cooperation units for Dermato-Oncology, Radiotherapeutical Oncology and Nuclear Medicine have meanwile been added. The Center also seeks to improve clinically oriented cancer research outside the university framework. It has now established a Clinical-Bio-medical Research Unit (Verbund Klinisch-Biomedizinische Forschung) together with appropriate major research institutes.

The complexity of cancer research requires the constant collaboration and exchange of ideas and experience between scientists in many professional disciplines, from both within and outside of the Center. Internally, the DKFZ currently has 1,600 employees, including 650 scientists in a wide variety of disciplines. Externally, it maintains numerous national contacts and cooperates with researchers from 30 foreign countries, including Israel. The DKFZ's Cancer Information Service, founded in 1986, provides professional information

to citizens over the telephone. Everyone can receive information, anonymously and free of charge, regarding all questions related to cancer by dialing 06221-410121. Since spring 1999 the Cancer Information Service can be found in the Internet. The entry is: http://www.krebsinformation.de

The Israeli Ministry of Science (MOS)

The Ministry of Science was founded in 1982 as the Ministry of Science and Development. Subsequent name changes - the Ministry of Science and Technology (1989), the Ministry of Science and the Arts (1992), the Ministry of Science (MOS, 1996) - have not changed its primary function, that of promoting strategic research that facilitates linkages between Israel's basic and industrial research communities. The National Council for Research and Development (NCRD), the MOS's predecessor, now serves as a broadly based national advisory committee. NCRD also helps the MOS formulate strategies for long-term national science and technology policy.

The promotion of science, of technological infrastructure and of international scientific cooperation have always been major features of Israel's Government policy - as envisioned 1946 by Chaim Weizmann, the famous chemist and President af the State of Israel

Science in Israel is comparatively decentralized, with specialized research and technology initiatives conducted under the Offices of the Chief Scientists of various ministries. In particular, industrial research is promoted by the Ministry of Industry and Trade. Funds for basic scientific research, which in Israel is largely (80 per cent) academic research, are provided by the Israel Science Foundation as well as by U.S.-Israeli (BSF) and German-Israeli (GIF) binational science foundations. The MOS concentrates its efforts on the missing link between the two, "strategic research", research too targeted to be called basic, yet still too far from immediate application to warrant industrial investment.

The MOS also coordinates various interministerial research committees; collects, analyzes and distributes information regarding Israeli research and development; and administers several active research grants programs (about 10 per cent of all

Israeli research). Since 1995, MOS has emphasized research in five priority areas: Advanced Materials Research, Biotechnology, Electrooptics, Microelectronics and Information Technology. A new program in the Biomedical Sciences is also under development. There is a marked trend towards supporting large strategic research and scientific infrastructure projects, rather than many smaller, untargeted research projects. This trend should provide the critical mass and strategic orientation required to further reduce the gap between basic and applied research.

The MOS maintains international scientific relations with over 30 countries and international organizations. German-Israeli scientific cooperation has flourished for decades, first under the NCRD and then under the MOS framework. The MOS Division for International Scientific Relations (MOS/ISR) helped found the semi-independent German-Israeli Foundation for Scientific Research (GIF) and maintains close contact with the activities of the Minerva Foundation Ltd., which is supported by the Max-Planck Society.

In 1976 the (then) BMFT and NCRD concluded an agreement to establish the German-Israeli Cooperative Program in Science and Technology. This multifaceted program is now jointly administered by MOS and the German Federal Ministry of Education and Research (BMBF, formerly the BMFT). This program's research projects in the natural and technical sciences are closely linked to special programs (Fachprogramme) and funding areas of the BMBF and to MOS scientific priorities. The cooperative research programs in each scientific area, e.g., in Biotechnology or Materials Research are administratively linked, on the German side, to national research centers (Großforschungseinrichtungen). The MOS/ISR acts as the Israeli administrative partner in all areas.

In the framework of the German-Israeli Program in Medical Research the DKFZ and NCRD signed an agreement in 1976 which initiated the current German-Israeli Cooperative Program in Cancer Research. This agreement sets down rules regarding the supervision, follow-up and financing of joint projects implemented by DKFZ scientists with partners from Israeli research institutes.

Israeli Research Institutes

Israel has seven major institutions of higher education, most of which are actively involved in state-of-the-art scientific research. Their student body, faculty and major interests are described below. Research at Israeli universities is partly financed by the Israel Government, through the Planning and Budgeting Committee (VATAT) of the Israel Council for Higher Education, and student fees. Research funds are also provided by MOS, the Israel Science Foundation and other grant programs. Scientific cooperation with foreign countries plays an important role in financing research and transferring knowledge.

The Israel Academic Community:
Major Research Institutions

Institution	Faculty	Students	Degree	Areas
Bar-Ilan University Ramat Gan	1300	17,000	BMP	LPS
Ben Gurion University Beersheva	795	9,400	BMPD	EHLPS
Hebrew University Jerusalem	2100	23,000	BMPD	HLPS
Rehovot (Agric.)	120			
Technion Haifa	700	10,600	BMPD	EHLP
Tel Aviv University Ramat Aviv	1800	25,000	BMPD	EHLPS
University of Haifa	800	10,000	BMP	LS
Weizmann Institute Rehovot	420	750	MP	LP

B = Bachelor, M = Master,
P = Ph.D, D = Medical Doctor (M.D.),
E = Engineering, H = Health/Medicine,
L = Life Sciences, P = Physical Sciences,
S = Social Sciences, Humanities, Law, etc.

The following paragraphs briefly describe the five main Israeli institutions which have participated, thus far, in the German-Israel Program in Cancer Research.

The Hebrew University

The rise of the Jewish national movement at the end of the last century increased the appreciation of the need for a Jewish university which would synthesize general learning and Jewish studies. The matter was raised by Dr. Chaim Weizmann in 1901 at the Fifth Zionist Congress. In 1902 Dr. Weizmann, Dr. Martin Buber and Dr. Berthold Feiwel published a pamphlet entitled "Eine Jüdische Hochschule" (A Jewish University) in which they laid the plans for such a university. The cornerstone of the Hebrew University (HU) was laid in 1918, and the University was officially opened in 1925. The HU's first Board of Governors, chaired by Dr. Chaim Weizmann, included Martin Buber, Sigmund Freud, Edmund Landau, Felix Warburg and Albert Einstein (who chaired the Academic Committee).

In the wake of Israel's War of Independence in 1948, the original Mount Scopus campus became inaccessible. After many years of provisional arrangements, the University built a new campus in Givat Ram near the center of town. This campus currently houses the HU Faculty of Mathematics and Natural Sciences, while the original Mount Scopus campus, accessible since 1967, now houses the Faculties of the Humanities, Social Sciences and Law. The Hebrew University-Hadassah Medical School (HUHMS), the first of Israel's four medical schools, was established jointly by the HU and the Hadassah Womens Zionist Organization of America in 1949, in provisional quarters. In 1965, it relocated to new facilities at Ein Kerem, on the outskirts of Jerusalem.

The two Hadassah teaching hospitals, at Ein Kerem and (since 1967) Mt. Scopus, are now part of the Hadassah Medical Organization (HMO). In addition to providing state-of-the-art medical care, the HMO is actively involved in medical education and research. Clinical and basic cancer research is pursued at many research centers within the HU and its affiliated hospitals. Typical topics include:

Molecular control and signaling pathways during normal differentiation and in carcinogenesis (including demethylation)

The function and regulation of oncogenes and suppressor genes. Molecular genetic changes in various cancer cells

Interaction of cancer cells with the extracellular matrix and the control of angiogenesis during tumor growth

Tyrphostins (selective tyrosine kinase inhibitors) as inhibitors of cancer cell growth

Liposomes for drug delivery

Immunological control of cancer growth and spread

Immunobiology of bone-marrow transplantation in cancer

Induction of programmed cell death (apoptosis) in cancer cells

The HU is actively engaged in world-class research in almost all areas of the natural sciences. It graduates about 28 per cent of all Israeli Ph.D.'s and carries out over a third of all civilian basic research in Israel.

The HU Faculty of Agriculture, which is Israel's only Faculty of Agriculture, occupies an impressive campus in Rehovot. One of their department deals with cancer in farm animals.

The Technion

The Technion - Israel Institute of Technology is located in Haifa, a major Israeli port on the Mediterranean. Formally inaugurated in 1924, its original building had been erected in 1912. Thus, like the Weizmann Institute of Science (Rehovot) and the Hebrew University (Jerusalem), the Technion was established before the State of Israel, dramatic testimony to the emphasis placed on science by Israel's original settlers and founders.

The Technion is Israel's premier engineering school. The source of most of Israel's engineers, its students (30 per cent graduate students) also

pursue a wide variety of subjects in the natural sciences, technology, and medicine. Clinically oriented cancer research is undertaken at the Rambam Medical Center and the Bnei Zion Medical Center, both affiliated with the Technion Faculty of Medicine.Two major foci of cancer research at the Technion are studies of:

The ubiquitin proteolytic system which plays a major role in modulating the activities of proteins like proto-oncogenes, tumor suppressors and cyclins.

Vascular endothelial growth factors (VEGF), which are highly specific mitogens for vascular endothelial cells and are important angiogenic factors.

The first class in drafting: Technion 1925

The ubiquitin system was first discovered at the Technion, and has been subsequently implicated in the degradation of several oncoproteins and wild-type p53 protein, both in vivo and in vitro. VEGF are produced by both normal and malignant cells and appear to play a major role in tumor angiogenesis (the formation of new blood vessels). Antibodies directed against VEGF can inhibit the growth of a variety of VEGF-producing tumors.

The Weizmann Institute

The idea of founding a world-class scientific research institute in (then) Palestine was raised in talks between Albert Einstein and Richard Willstätter in the 1920s. The institute was to be unique, in that it would be self-administered and bound only by the standard of its scientific quality. This concept was later discussed with Fritz Haber. The famous chemist and Zionist leader, Dr. Chaim Weizmann, took up this idea, which was first realized in Germany with the founding of the Kaiser-Wilhelm Institutes (later the Max-Planck Institutes). In Israel, this goal has been realized in the current Weizmann Institute of Science (WI) which is a full-time research institute, rather than a traditional university. Founded in 1946, the WI grew out of the far more practically oriented Daniel-Sieff-Institute. Established in 1934 by British philanthropists, the Sieff Institute's original interests were industrial bacteriology and pharmaceutical and agricultural chemistry. (Chaim Weizmann was, himself, the first Director). The institute's name was changed in 1949, and Dr. Weizmann simultaneously served as Director of the Institute and President of the State of Israel for some time.

Today the WI is a well-known, world-class scientific research center. More than half the scientific work in the Institute's Faculties of Biology, Biochemistry, Chemistry, Physics and Mathematical Sciences is, in some way, connected with cancer research.

WI cancer researchers have, over the years, made many outstanding contributions to cancer research. Among their more recent contributions is the demonstration that disrupting the genes that produce vinculin and α-actin increases cancer cell motility and tumorigenesis, while increasing the production of these proteins suppresses tumorigenicity. Other Weizmann Institute scientists are studying how rearrangments of the ALL-1 oncogene, and its newly discovered ALR analog, can lead to acute lymphatic leukemia. Another study elucidates the complex, orderly signaling network formed by the Erb B family of transmembrane growth factor receptors. Three levels of signal diversification permit the stringent control of mitogenic and differen-

tiation signals. Another researcher has shown how heparan-sulfate proteoglycans serve as obligatory accessory receptors for growth factors such as FGF and tightly regulate cell growth and fate.

Defects in the p53 gene are found in over 60 per cent of all human tumors. Pioneering WI research on this gene is particularly well-known. It is now thought that normal p53 halts cell replication during the cell's "resting phase" to permit correction of DNA errors prior to cell division. The researchers have shown that the C-terminus end of the p53 protein senses damaged DNA and triggers repair mechanisms. When errors in the DNA are too numerous to fix, p53 initiates programmed cell death (apoptosis). Five novel genes and a known protease were shown to play a part in interferon-induced apoptotic pathways. These Death Associated Protein (DAP) genes were discovered using anti-sense inactivation techniques.

Other WI researchers have identified tumor-associated antigen (TAA) peptides, studied their role in metastasis and successfully tested a TAA-based, anti-metastatic vaccine in mice. Others are using MRS (magnetic resonance spectroscopy) microscopy to study the formation of the new blood vessels (angiogenesis) that are essential to tumor growth, and to develop diagnostic tests to distinguish between benign and malignant breast lesions.

In his autobiography, "Trial and Error", Weizmann comments on the Institute's deliberate concern for esthetic beauty. "When the Institute was built it looked as if we were going to sink into a sea of sand ... After two or three years of care, the whole was transformed into a garden which delights the eye and every visitor and worker feels the effect." Today the Institute's forty buildings are spread out over a subtropical green campus more than a square kilometer in size.

The Tel Aviv University

In 1956 three smaller Tel Aviv-based research institutes were combined to form the Tel Aviv University (TAU). The TAU Faculty of Medicine was founded in 1964 on the Ramat Aviv campus with the participation of major local hospitals, such as Ichilov Hospital (part of the Elias Sourasky Tel Aviv Medical Center) and the Chaim Sheba Medical Center (Tel Hashomer), Israel's largest medical center. During the next decade many new faculties were established (at present it has 9 faculties and 90 departments). TAU is now Israel's largest research and teaching center.

TAU has one of Israel's largest concentrations of basic scientists and clinicians engaged in cancer research, including almost 100 scientists and physicians from the George S. Wise Faculty of Life Sciences and the Sackler Faculty of Medicine. They perform clinical, preclinical and basic research on biological, molecular, genetic, immunological, virological and environmental aspects of the disease.

In order to promote multidisciplinary cooperation TAU has established a Cancer Biology Research Center. The Center uses proceeds from its cancer research endowments to fund "starter grants". The Center holds an annual conference which provides a forum for the exchange of information and data from 200-250 researchers from laboratories, university-affiliated hospitals, large medical centers and small community health services, fostering the cross-fertilization to which the Center is dedicated. These annual meetings are supported in part by the Israel Cancer Society.

TAU also operates two academic cancer research institutes: the Ela Kodesz Institute for Research on Cancer Development and Prevention, in the Faculty of Life Sciences, and the Stanley Steyer Institute for Cancer Epidemiology, in the Faculty of Medicine. In addition, the University holds an annual Otto Herz Lecture Series in Cancer Research, which brings distinguished scientists from abroad to present lectures and seminars. In 1992 an International Symposium was held to mark the tenth anniversary of this series.

The Ben-Gurion University of the Negev

The Ben-Gurion University of the Negev (BGU), Israel's youngest university (founded 1969), is located in Beer-Sheba, a town just north of the Negev Desert. The development of arid lands agriculture and other desert related topics were among the university's original research priorities. Another important priority is health-related research to benefit the population of south Israel. This research is carried out at the university's Medical School (founded 1973). The university has grown rapidly,

and is now active in almost all areas of modern science.

BGU has established a broadly based interdisciplinary Cancer Research Center which lists more than 70 scientists and research clinicians as active members. Members of the Center include the: Institute of Clinical Oncology, Institute of Pathology, Division of Basic Sciences, Division of Surgery and the Departments of Chemistry and Physics. Research teams pursue priority topics in both basic and clinical oncology, including: molecular oncology, metastasis, tumor immunology and immunotherapy, modifiers of cancer therapy, multiple drug resistance, oncological virology, signal transduction, cell cycle regulation and apoptosis, the enzymology of DNA repair, early detection, epidemiology and radiation and chemical hazards.

The University's Sede Boker campus, deep in the Negev Desert, is the home of the Ben-Gurion Research Institute and the Jacob Blaustein Institute of Desert Research. David Ben-Gurion and his wife are buried on a hill high above the university which is named after him.

The Preliminaries

"One Plus One Can Be More Than Two"

An interview with the coordinators

The following chapter is adapted from interviews with Prof. Erich Hecker and Dr. Yair Degani, respectively the German and Israeli Coordinators of the German-Israeli Cooperative Program in Cancer Research. Here they discuss the history and development of the current program

Since the program's beginning in 1976, Professor Erich Hecker has served as Vice Chairman of the Program Committee and as the program's Coordinator at the DKFZ. He has served as Chairman of the DKFZ Board of Directors (1970-1971) and President of the DKFZ Scientific Council (1973-1977). He is now Professor Emeritus in Biochemistry

In 1959 the Max Planck Society and the Weizmann Institute initiated jointly the German-Israeli scientific relations, mainly in physics and chemistry. Who played a similar role in developing German-Israeli collaboration in cancer research?

Hecker:
In 1974 the Weizmann Institute's European representatives in Zürich invited DKFZ representatives to visit Israel. I was then the Chairman of the DKFZ Scientific Council and Professor Klaus Munk the Chairman of the DKFZ Management Board. Once there, we visited many research centers, especially the Weizmann Institute and the Hebrew University. One evening, over a glass of wine, we discussed the problem of how to finance science in order to further its development. In Israel, the concentration of gifted researchers is particularly high and, of course, it was desirable to help prevent such talent from leaving the country to seek more lucrative opportunities elsewhere.

Once back in Germany we felt obliged to examine the possibility of collaborating with Israel. This idea, however, fell outside most existing mechanisms. The Max Planck Society was (then) not interested in cancer research, while the German Research Society (DFG) was unable to assist us for statutory reasons. The German Federal Minister for Research expressed great interest; but he had no available funds. When we informed our Israeli partners of the situation, they succeeded in interesting members of the Budget Committee of the Bundestag, particularly the Deputy responsible for biomedical research. The Budget Committee eventually allocated DM 600,000 per year to the Ministry for Research to be transferred to Israel through the DKFZ for scientific cooperation in cancer research. The subsequent cooperative agreement became the framework for our collaboration.

Dr. Yair Degani, a biochemist, is the Head of the Division of Life Sciences at the Israeli Ministry of Science. He was previously a Senior Scientist at the Weizmann Institute (Rehovot)

What was Germany's interest in this agreement?

Hecker:
One should look at this collaboration in the light of German efforts to reach a reasonable relationship with the Jewish people and the State of Israel after World War II. There was a readiness to do something for Israel and also recognition of the outstanding research being done there. The agreement states that the DKFZ would be receiving expert knowledge, from Israel, thanks to the funds supplied. Collaboration means that one and one is really more than two, provided the collaboration is successful. Science is particularly suited to bringing people together, even if they have completely different political views.

What was Israel's interest in this agreement?

Degani:
As a small country which seeks to maintain its scientific research activity at world-class standards, Israel finds international scientific cooperation particularly vital in several respects. Joint research programs and cost-sharing help stretch Israel's limited research budget. Constant interaction and collaboration with scientists abroad provides intellectual synergism with a large pool of international talent and improves research performance.

In the absence of relations with her immediate geographical neighbors during the State's first decades, Israel's most natural choice for collaboration was the relatively close-by scientific community of Europe, with which many Israelis shared a common cultural and historical background. Germany has always been a major scientific power in Europe. German scientific research has expanded continuously, thanks to the German Government's heavy investments in research. Germany also played a central role in many international European organizations which Israel sought to join. The willingness of Germany to cooperate with Israel in science and technology was welcomed by Israel's National Council for Research and Development (NCRD) and other leaders of Israel's scientific community. The German-Israel Cooperative Program in Medical Research, of which cancer research is a major part, was of special significance to Israel. Medical research expresses universal values, which touch the life of every human being. Disease, illness and death do not recognize national, political or geographical boundaries, and all nations seek to improve the health of their citizens, so no other area of scientific activity could be more fitting for international cooperation.

How did the organization of the cooperation develop?

Hecker:
Fruitful collaboration in a multidisciplinary field such as cancer research can only be implemented through individual projects in which scientists work together on a one-to-one basis. The first six projects were, so to speak, conjured up from nowhere without any special infrastructure. The agreement signed between the German Federal Ministry of Reserch and Technology (now BMBF), DKFZ and the Israeli National Council for Research and Development (now MOS) in 1976 left to the partners the task of elaborating the details of this collaboration. As a member of the DKFZ Scientific Council, I had long been interested in international cooperation and was particularly fascinated by Israel. I was quite willing to travel there to consult with our Israeli partners on how to best implement such cooperation. That was in 1978, by which time I had already obtained valuable practical experience from cooperative projects with Thailand and Egypt.

What happened at that time?

Hecker:
In our discussion, one could clearly sense the reserve of the Israelis. One problem was that, since superior research scientists from both sides were to participate, it was necessary to lay down firm criteria of quality. Israel is, however, a small country; and Israeli scientists were reluctant to evaluate their fellow colleagues who had made applications.

My own attitude during these talks, which could be called the first meeting of the Program Committee, was that cooperation could be implemented only if both sides participated with complete equality of rights and not if the side providing the funds came with the motto: "the one who pays, makes the rules." When it became clear that we needed a Program Committee, I proposed that it be composed of equal numbers of Israeli and German (or other European) scientists, including one Coordinator from each side. The Program Committee would meet once a year, alternately in Israel and in Germany. The Chairman, elected from among the members of the Committee, would serve for only one year.

How did the Program's structures develop?

Hecker:
Most structures developed over time, one by one. At the next Program Committee meeting in Germany, we drafted a paper outlining how to generate and choose projects. The Israeli side felt that such a cooperation should constantly develop. That is why the paper is still called: "Temporary Procedures to Generate Common Projects." It took us about ten years in order to fully develop these "Temporary Procedures". They were continuously perfected, based on our experience.

Degani:
For example, at the beginning we didn't have a Joint Concluding Report, only the standard annual reports for each partner. Later we decided to request a formal Joint Concluding Report, co-authored and co-signed by the Israeli and German partners, without fixing its format. That proved to be insufficient and we eventually realized that it would be useful to specify a special form for the report, to ensure that it contained all the information required. The final format specifies exactly what

should be written on which page, in which sections. We extensively advise the investigators of both partner organizations and, at an earlier stage, can even help them find potential partners.

What has been the program's recipe for success, on both the personal and scientific level?

Hecker:
Friendship cannot be prescribed. We can only remind the researchers that fruitful scientific co-operation requires the personal exchange of ideas and that it is important to undertake reciprocal visits and joint experiments. The Program Committee considers it essential to provide travel funds for each subproject. Experience has repeatedly shown that the most fruitful ideas, ideas which result in further experiments, often arise by chance, over a casual cup of coffee or in the evening after supper.

At least once during the three years of each project, the project's partners participate together in a workshop. At these Status Seminars the researchers present joint reports regarding all active projects to the Program Committee in the presence of a selected audience of fellow scientists. Furthermore, the Program Committee is briefed on the progress of each project at its annual meeting. One year the Israeli partners report to the Committee (when meeting in Israel); the next year the German partners report to the Committee (when meeting in Germany). Even so, the partners still do not always collaborate as closely as we would like.

What sort of things can go wrong?

Degani:
For example, one project had no publications; and I asked the investigator what had happened. There was a problem with certain cells one partner was to supply. They were not exactly the right type, something was wrong with them, and no publishable results had been achieved. This can sometimes happen; there is no 100 per cent guarantee for success.

On a broader level, we once included several epidemiological topics among our priority areas. We eventually realized that epidemiological projects are not well-suited for this kind of program. For example, such projects often require far more than three years in order to yield meaningful results, whereas our projects are limited to three years duration. This is a serious limitation since, according to the "Temporary Procedures," an Israeli grantee cannot receive another grant before having abstained for three years (this restriction does not apply to German grantees).

However, these original epidemiology projects were not necessarily failures. When we were updating our lists of publications, both for the Program's twentieth anniversary in 1996 and for its international evaluation in 1997, we found many new publications arising from these projects, even five years after their termination. Thus, in some cases, the fruits of those original epidemiology projects are merely ripening late.

What standing does this cooperation have?

Degani:
In Israel, the Cooperative Program is well-known and highly regarded, both for its scientific results and for its scientific management by the Program Committee and its Coordinators. About five years ago the Program's budget was increased almost 40 per cent by additional contributions from the DKFZ Management Board, over and above the BMBF's allocation. This itself reflects the widespread recognition of the success of this program within the DKFZ, especially at a time when research budgets are becoming tighter and more restricted.

How does the Cancer Research Program compare with other programs in the German-Israeli Cooperation?

Degani:
In several respects, cooperation between scientists in the Cancer Research Program is more developed than in other areas of the overall BMBF-MOS Cooperative Research Program. So are the structure, procedures and management of this program, particularly the way it is supervised by the Program Committee. One basic difference is that this program also funds German scientists. In most other BMBF-MOS subprograms, German scientists receive only travel funds, which makes it more difficult for the partners to work together. This is changing now; and other subprograms are begin-

ning to fund the German side as well. This is a good development, one which we have tried to encourage for many years.

What aspects of the Cancer Program can serve as a model for others?

Hecker:
The BMBF and MOS are setting up international evaluation teams to analyze how well the cooperative projects in all of their joint programs function. In general, the individual Program Committees decide how to structure and control the collaboration. As a general rule, the intense interaction found among the cancer researchers is not found in the other BMBF-MOS cooperative programs. In the DKFZ-MOS Cooperative Program in Cancer Research, the Program Committee plays a very special supervisory role.

Ilana Lowi (middle) was Deputy Director of the MOS Division for International Scientific Relations (MOS/ISR) until 1996. Nurit Topaz (right) heads the MOS/ISR Section for Scientific Relations with Germany

Lowi:
MOS international research programs have adopted a number of procedures which originated in the Cancer Research Program. One example is the 2n Selection procedure, in which the Program Committee receives up to twice as many proposals for final evaluation and selection as can be funded.

Topaz:
All of the BMBF-MOS subprograms have either a Program Committee or an Advisory Committee. The difference is that a Program Committee actually makes decisions, while the Advisory Committee can only give advice, leaving final decisions to the relevant ministries. The Cancer Research Program's strong Program Committee gives it a definite advantage.

What is the primary motivation for this German-Israeli undertaking? Increasing understanding between the two nations?

Hecker:
From a political point of view that has, no doubt, played an important role, particularly in motivating financing. On the scientific level, however, collaboration with Israel has been particularly effective in demonstrating the multidisciplinary character of the DKFZ's scientific endeavors and making these internationally known.

Degani:
The development of German-Israeli relations has been a matter of great delicacy. In the early years of the German-Israeli Cooperative Program, there were some Israeli scientists who, for emotional reasons, refused to take any part in the program, either as applicants for research grants or as reviewers of applications submitted by others. Over the years such cases have become increasingly rare. Many of us feel that the cooperative activities of the program have greatly contributed to building a bridge over that gulf of hatred and grief. From the scientific point of view, the contacts created through this program have proved, over the years, to be highly productive and of mutual benefit to both sides. This has laid a firm foundation for long-term professional cooperation.

Does one notice in the cooperation that the relation between the two countries is a special one?

Hecker:
Not any more. Emotionally speaking relations are now very close to normal. At the program's beginning in 1976, the Israelis were extremely reserved, but this should not be understood primarily as a reserve towards German researchers. It was largely a more general reserve towards the kind of collaboration represented by this program. The program demanded real cooperation rather than the separate development of similar, but parallel, projects. It demanded considerable personal contact and an special forthcoming personality. In the beginning collaboration with German scientists was doubtless a special component, but it really does not seem so today.

The Program

Flexible Routines

The ”Temporary Procedure to Generate Common Projects” are always open to changes

Before each new Call-for-Proposals in priority topics, the DKFZ Scientific Council first discusses its proposed priorities with the Management Board of the DKFZ and then proposes them to the Israeli side. MOS and the Israeli members of the Program Committee discuss the proposed research priorities, and may introduce their own proposals, in the light of Israel’s cancer research priorities.

A final decision is made jointly, after joint discussion, at the annual Program Committee meeting. Priorities are announced about one year before the planned beginning of the research. The Call-for-Proposals is circulated in the DKFZ and in Israeli research institutes. The Israeli Ministry of Science also distributes information regarding the DKFZ and its activities throughout Israel. This includes reports on DKFZ research and description of available DKFZ publications.

The three priority topics chosen for the most recent call-for-proposals (research to begin on January 1, 1998) are the:

Regulation of cell proliferation and differentiation in normal and neoplastic cells.

Role of viruses in the control of malignancy in human cells.

Mechanisms of increased and/or selective toxicity for cancer cells through apoptosis (programmed cell death).

In response to the Call-for-Proposals, a great number of scientists submit applications for projects. Every proposed project must consist of complementary German and Israeli subprojects. The researchers often know each other from international scientific conferences they attended or through mutual colleagues. If this is not the case, the Program Coordinators, with their vast experience, can assist in the search for potential scientific partners. About 25 to 30 project proposals are submitted each year by Israeli investigators. These are then forwarded to expert referees for external peer review, both in Israel and abroad (mostly in Europe and the U.S.A.). On the basis of the written evaluations submitted by the reviewers, the Israeli members of the Program Committee choose twice as many project proposals as can be financed (the so-called 2n selection procedure approach). The corresponding German subproject proposals are evaluated by the DKFZ Scientific Council.

The Program Committee discusses and evaluates these 2n proposals - usually 12 to 14 proposals at a time - and ranks them using a point system which takes several criteria into account. One of the most important criteria for the choice is the probability of fruitful collaboration. Other criteria are originality, scientific quality, and significance to advancing cancer research, adequacy of the proposed methodology and the project’s cost/benefit ratio. About six to seven projects (“N”) are finally chosen for three-year support.

The Program’s Coordinators:
Erich Hecker (left) and Yair Degani

The Research Areas

Despite their high degree of diversity, the 61 research projects supported by the DKFZ-MOS Cooperative Program in Cancer Research over the last two decades fall within six broad areas corresponding, to a large extent, to the research priorities of the DKFZ. These are described below.

Cell on Cell

Thirteen projects in the area of
"Cell Differentiation and Carcinogenesis"

Differentiation is the process by which cells specialize, so they can perform specific tasks. Cancer cells often no longer perform the specialized tasks which characterized their healthy precursors. Carcinogenesis begins with changes in the genetic material, DNA. Such mutations can be induced by external agents or can arise spontaneously. Such mutations can activate some cancer-associated genes (oncogenes) at the wrong time or, alternatively, they can inactivate important control (regulatory) genes, including tumor suppressor genes.

Scientists can now use advanced cell biology and genetic engineering methods to find out where such genes are located on the chromosomes, the biochemical signals they switch on or off and the mechanisms by which they interrupt the finely balanced genetic mechanisms controlling cell growth. Researchers can also analyze the proteins whose structural information is coded in these genes, and search for their occurrence in various pathological and normal cell types. Most cells are organized in large associations called tissues. In the case of cancer cells, however, the carefully regulated contact points which usually connect the cells to each other and to their environment are often changed or damaged. That is why cancer cells can break out from their tissue of origin, migrate to other sites in the body and there create secondary tumors (metastases).

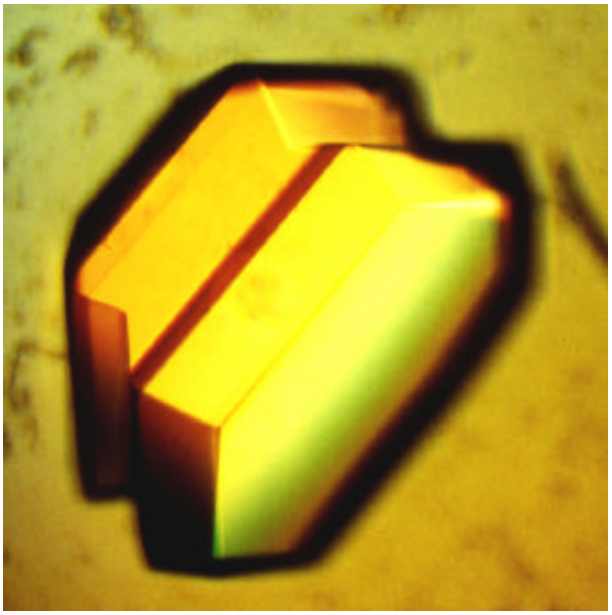
A project concluded in 1993 by Professor Werner Franke, Head of the DKFZ Division for Cell Biology, and Professor Benjamin Geiger, Department for Chemical Immunology at the Weizmann Institute of Science, has enhanced our knowledge of the molecular components of the important structures that maintain cell-cell contact and the changes that accompany cancer and metastasis. Their joint project was entitled: "Structure-Function Relationships in Adhering Cell Junctions of Normal and Transformed Cells." The researchers discovered, among other things, a new type of intercellular contact molecules (complex adherents) in endothelial cells which line the blood and lymph vessels.

Professor Eli Keshet of the Department of Molecular Biology at the Hebrew University-Hadassah Medical School has examined the role of endothelial cells in developing the structures needed to supply blood to a growing tumor. His scientific partner in this project on the "Regulation of Proteases and their Respective Inhibitors Mediating Cell Invasiveness During Angiogenesis and Metastasis," successfully completed in mid-1996, was Professor Eberhard Spiess, Head of the DKFZ Study Group on Biomedical Structure Research. Spiess, using confocal laser scanning and conventional light microscopy, examined cancer cells of the lung which penetrated neighbouring collagen structures, their first step towards escaping from their original tumor. Spiess succeeded in visualizing, for the first time, the "weapons" of the cancer cells, their protein digesting enzymes (proteases), during their invasion. Using the visualization techniques of the Heidelberg laboratory, Keshet demonstrated the key role of specific protease activators and their conjugate inhibitors in the control of blood vessel invasion into expanding tumors.

The Switch of Life

Eleven projects in the area of
"Tumor Cell Regulation"

Many genetic changes which lead to cancer hamper the communication between cells, tissues and the entire organism. Communication is necessary for maintaining the proper functioning of that finely balanced division of responsibilities that characterize the body. Cellular communication is based mainly on the exchange of chemical signals such as hormones, growth factors, neurotransmitters, cytokines and other mediators. The target cell has to notice and respond to the chemical signal it receives on its surface, where each chemical signal binds to a specific (exactly fitting) receptor molecule. The signal, once detected, must be transferred to the inside of the cell (often in quite a different form); there the secondary message is interpreted and used to trigger an appropriate response. The signal can, for example, switch off or



Crystals of protein kinase A, a key cellular enzyme

on biocatalysts or genes, modulate the cytoskeleton, alter the permeability of the cell membranes and boost or block the replication of cells.

A central role in processing such signals is played by enzymes which transfer phosphate groups to proteins (kinases) or which split off phosphate groups from proteins (phosphatases). Disruptions in this universal biochemical switch can have fatal results for the cells. Many proto-oncogenes, the undamaged precursors of cancer genes, contain the structural information required to produce specific kinases. The manifold modes of signal transduction are interlinked with each other and feedback-coupled, since a healthy cell has to switch signals off again.

Excessive phosphorylation of an important regulatory protein can explain why transformed keratinocytes (skin-tumor cells), no longer respond to a chemical “stop signal” (TGF-β) and multiply without control. This was observed by Professor Adi Kimchi of the Weizmann Institute of Science and Professor Norbert Fusenig, Head of the DKFZ Division of Differentiation and Carcinogenesis In Vitro. Their project “Negative-regulating Growth Factors and the Significance of their Abrogation in Carcinogenesis” was concluded in 1996. Knowledge of how molecular mechanisms can alter a cancer cell’s reactions to chemical signals, may eventually permit influencing the development of tumors.

Early Detection and Prevention

Four projects in the area of
”Cancer Risk Factors and Prevention”

External factors play a causative role in most forms of cancer. According to recent risk estimates, smoking and improper diet each cause about one-third of all cancers. Up to eight percent are related to harmful influences in the workplace; two percent, to harmful environmental factors such as ultraviolet light from the sun.

A high vitamin C supply, for example by fruit and vegetables, diminishes the risk of stomach cancer

Cancer prevention includes both the exclusion or reduction of risk factors (primary prevention) and the early detection and interruption of disease development. This requires an awareness of risk factors, their potential dangers and their mechanisms of action. Information on how environmental influences can affect the frequency of cancer is derived from epidemiological studies. These studies uncover differences in the incidence of various forms of cancer between populations differing in their location, time, gender, occupations, habits and ethnic origin. Scientists can thus estimate the cancer risks of particular substances or groups of substances to which people are exposed in their professions or lifestyles. The latter include the effects of smoking and diet.

Using molecular biological, toxicological and pathological methods, scientists study the development

of externally caused tumors, which must be detected above the background of malignancies caused by endogenous influences. Errors in the hereditary material DNA can be introduced during normal DNA-replication which precedes cell division, and they can be inherited as a genetic predisposition for cancer. More information on the early stages of cancer and the mechanisms of carcinogenesis is required to develop better and more effective cancer therapies.

Benefit for Patients

Five projects in the area of
”Diagnostics and Experimental Therapy”

“It will remain the laborious but not hopeless task of experimental therapy to continually discover, for practical purposes, new types of effective substances.” So wrote Paul Ehrlich at the beginning of the century. Although he had developed a chemotherapeutic treatment against syphilis through systematic scientific experiments, the search for new therapeutic procedures for cancer proved to be far more complex.

A tumor develops from changed body cells which multiply in a disorderly and unhampered fashion; it is thus not a tissue foreign to the body. Depending on which body cells transform into tumor cells, quite different cancerous diseases develop. These take different courses and present different possibilities for treatment.

Many small steps forward - and close cooperation between basic research and clinical medicine - are necessary in order to use the new knowledge gained in the laboratory to benefit the patient. In projects of the DKFZ-MOS joint program on “Diagnostic and Experimental Therapy,” cancer scientists and physicians have worked together on concepts related to adjuvant radio-, chemo- and immuno-therapy. They have studied the biological activity of certain immune complexes in breast cancer patients, and they have sensitized immune cells to enable them to resist cancer. Others, such as molecular biologists Manfred Schwab and Moshe Oren (see page 86), have started clarifying the mode of action of the cancer-suppressing gene p53. The results of the Schwab-Oren collaboration could eventually be useful for improving radiation therapy.

Metastasis, of Jörg Drühl

Borrowed Life

Eleven projects in the area of
”Applied Tumor Virology”

The scientific world had long considered the research of the American pathologist Peyton Rous on poultry viruses as a biological curiosity without great significance. Rous had, in 1911, drawn attention to the possible role of viruses in the development of tumors in domestic fowl. In 1966 he was awarded the Nobel Prize in Medicine for his pioneering experimental results.

At present four groups of viruses are known to contribute to the development of specific malignant diseases in humans. These include the hepatitis B virus, a herpes virus (Epstein Barr virus), two Papilloma viruses (which induce cancer of the uterine cervix) and several retroviruses.

A virus particle, which is only about one ten thousandth of a millimeter long, consists of genetic material (DNA or RNA) encapsulated in a protein envelope. Since it does not have its own metabolic machinery, it can multiply only in living cells, where it makes its unwitting host provide the raw materials and “technology” for making more copies of its uninvited guest. In many cases the host cell is not damaged; however, when the virus incorporates its genetic information into the host cell’s genome, cancer can result. The ways in which some viral genes disturb the growth control of their host cells so seriously that they become cancerous are varied. As a general rule, infection with a tumor virus does not suffice to cause carcinogenesis. Usually there

must be a secondary "trigger," such as carcinogenic chemicals, radiation or special genetic structures in the host cell. A joint project successfully completed in 1994 by a team of German and Israeli virologists, Rolf Flügel and Mordechai Aboud, has clarified how such additional factors affect the development of virus-induced cancer (see page 84).

The identification of viral cancer risk factors contributes to the search for new diagnostic and therapeutic processes. It is already possible to prevent liver cancer by immunization with hepatitis virus and there is a hope of extending this success to other virus-induced tumors. Cancer viruses are also useful in basic research on how normal cells are converted to cancerous ones. Scientists further hope to utilize the ability of viruses to insert foreign genes into the genome of human cells for gene therapy.

Harnessing Defense Mechanisms

Seventeen projects in the area of
Tumor Immunology

The cancer cell culture "melted like butter in the sun" reported Lloyd Old, an American immunologist in 1975. He had added a small, naturally occurring (endogenous) protein to his culture and the results had been amazing. He named this now world famous protein "tumor necrosis factor (TNF)" from the Greek word necrosis, "to die off". Biologists and physicians have shown that the observed destruction of tumor cells in vitro cannot be easily replicated in man. In man, TNF's modes of action and signaling pathways are much more complex, even somewhat contradictory. The joint DKFZ-MOS project: "Mechanisms Controlling the Response to Tumor Necrosis Factor" has contributed considerably to a detailed molecular analysis of how cells respond to TNF. The three scientists involved worked together in close cooperation during 1989-1991. The team consisted of David Wallach of the Weizmann Institute of Science (Rehovot), Daniela Männel of the DKFZ Division of Immunochemistry and Helmut Holtmann of the Medical College of Hannover. Holtmann's participation was somewhat unusual, as he was a non-DKFZ German partner.

Tumor cells differ from their healthy counterpart in many different ways, and they hide from the "watchdogs" of the body's immune system in many different ways. Accordingly the points of departure are different. Over the last decade immunologists discovered that some of the immune system's defense cells do not simply produce antibodies which mark the foreign body in ways that attract other cellular "soldiers" of the immune system. In addition, these defense cells can release hormones and other chemical messengers which direct the subsequent immunoreaction and related cell functions in a very complex manner.

Scientists now understand some routes by which the immune system's "police" cells recognize and destroy cancerous cells. This defense system is, however, often overtaxed in the case of an advanced tumor. The immune system seems better able to combat smaller numbers of isolated cancer cells. That is why some new immuno-therapies concentrate on fighting metastases, small secondary tumors which develop from roving free cancer cells.

Our basic knowledge of how immune cells from the bloodstream can penetrate other tissues was greatly enhanced by the joint DKFZ-MOS project of Israel Vlodavsky and Volker Schirrmacher in the mid-1980s (see the following page).

Research Results

The Scientific Program Committee chose seven "highlight projects" of the cooperation program out of 61 joint projects (1976 - 1996). The awards for the projects Ca 24, Ca 41, Ca 49, Ca 50, Ca 51, Ca 58 and Ca 59 (see Appendix) were handed over to the investigators in March 1997 when the 20th anniversary of the cooperation program was celebrated, in conjunction with the seventh workshop of the cooperation program. Three of these highlight projects are illustrated below.

Making the Invasion Visible

Project Ca 24 showed for the first time how metastasing cells leave the blood vessels

In 1972 DKFZ biochemist Volker Schirrmacher traveled to Israel to attend a Summer School course at the Weizmann Institute of Science in Rehovot. These memorable weeks were the start of a continuous tie between Professor Schirrmacher and Israel, both the country and its people. Further visits and contacts with Israel's "pragmatic and innovative researchers" followed. With the initiation of the DKFZ-MOS Cooperative Program in Cancer Research in 1976, Schirrmacher, by then Head of the DKFZ Division of Cellular Immunology, became "a permanent visitor" in Israel.

Since that time Schirrmacher has participated in, and successfully completed, six joint projects. One of these was Project Ca 24, undertaken with Professor Israel Vlodavsky. The collaboration, which began on January 1, 1983, was a landmark, pioneering investigation of metastasis, the process by which tumor cells leave their original tumor, travel through the bloodstream and invade and colonize new tissues. Such metastasis results in new tumors "beyond" (Greek, meta) the site of the original tumor.

The original tumor can, in many cases, be removed surgically or treated by chemotherapy or radiation. In contrast, metastases in other organs are usually only detected after they are too numerous and widespread to permit a cure. New knowledge about how metastases form may provide important new points of departure for the development of improved cancer therapies. The results of this successful collaborative project have greatly increased our knowledge of how cancer cells succeed in leaving blood vessels to invade healthy tissue.

Israel Vlodavski, Hadassah Medical School, with a student

The story of Project Ca 24 begins with Vlodavsky's return to Israel in 1980, after a three-year post-doctoral appointment in the U.S.. Back in Jerusalem he set up a tumor biology research laboratory at the Hadassah-Hebrew University Hospital. Vlodavsky was an expert in endothelial cells that line the inside of blood vessels and he asked his Israeli mentor, Zvi Fuks, to suggest someone knowledgeable in tumor cell invasion and metastasis. Fuks referred him to Schirrmacher, who had developed a unique experimental system consisting of highly metastasizing lymphoma tumor cells and their parental counterpart, cells that show little urge to spread.

Vlodavsky recalls that "it was a good idea to adopt Schirrmacher's system and to include it in our research". Working together, the scientists obtained exciting electron microscope pictures which showed how tumor cells break the close contact between endothelial cells and, then, by an extreme change in form, squeeze in between them and eventually escape the endothelial cell lining of blood vessels. (see page 34)

Further laboratory studies on the cultures of aortic endothelial cells cast light on the role of the sub-endothelial extracellular matrix (ECM). The cells divided in plastic culture dishes, until the bottom of the dish was covered by a thin layer of cells. Under the influence of a cocktail of specific growth-promoting factors, these cells began producing, on their underside, an ECM. The ECM, an impenetrable net-like layer composed of macromolecules such as collagen and complex saccharides, was similar to that found in the vessel wall.

Vlodavsky traveled for two weeks to Heidelberg at the beginning of his DKFZ-MOS project in order to learn more about Schirrmacher's research on tumor metastasis. This visit was followed by several other visits of the principal investigators and other members of their teams in the Israeli and German laboratories. Both teams quickly realized the enormous potential of this model system. They soon found that cancer cells adhere much better to the ECM than to the endothelial surface. This difference was more prominent when a slight shaking of the culture dish was applied to imitate the passing blood flow in the intact blood vessel, leaving more time for the circulating defense cells to fight the invading cancer cells.

How can a tumor cell pierce the ECM? To answer this question Vlodavsky and Schirrmacher first developed a radioactive labeling technique that is still in use. They fed endothelial cells radioactive substances, which they subsequently incorporated into their ECM. The endothelial cells were then washed off the underlying ECM using a detergent. The researchers then added intact tumor cells or tumor cell extracts and studied how these affected the exposed ECM. Their experiments showed that cancer cells "cut" their way through the ECM's protective network in an enzymatic way.

The radioactively marked ECM fragments released in this process were then separated by gel filtration, according to their sizes. The researchers found that, unlike poorly metastasizing cancer cells, the highly metastasizing variant produced smaller fragments. These fragments resulted from the action of a specific enzyme (heparanase) which cuts into small pieces the long chain-like molecules of the sugar heparan sulfate proteoglycan, an important component of the ECM. Heparan sulfate proteoglycans interact with various components of the ECM and stabilize its network structure and barrier properties. ECM degradation increased when protein digesting enzymes, such as plasminogen activator and plasmin were added to the system. These proteases seemed to break open the ECM, facilitating the entrance and action of heparanase.

While Schirrmacher went on to study cancer cell metastasis, immunobiology and immunotherapy, Vlodavsky and his colleagues (Atzmon, Bar-Ner, Ishai-Michaeli) continued to research the heparanase. They followed two distinct strategies. First, they designed and produced substances which inhibit the enzyme, making it difficult for cancer cells to colonize other tissues. Second, they tried to purify and clone the heparanase protein and studied the regulation of its expression and tissue distribution. These lengthy experiments have confirmed what Vladovsky and Schirrmacher's pioneering electron microscope studies revealed in the eighties: cancer cells penetrate the vascular wall the same way the body's own defense cells (i.e., white blood cells) leave the bloodstream to search nearby tissues for foreign matter. Moreover, heparin-like substances which inhibit the heparanase enzyme also inhibited lung colonization of melanoma and breast carcinoma cells in experimental animal models.

In subsequent studies performed in 1986 in collaboration with Profs. Folkman and Klagsburn (Harvard Medical School), Vlodavsky identified a new role for heparanase in tumor progression. A growth factor is usually tightly connected to the heparan sulphate molecules found in the ECM. This factor can stimulate the growth of new blood vessels (angiogenesis) which are needed to supply a growing tumor with essential nutrients and oxygen. However, the growth factor can best induce angiogenesis when it is released from its storage in the ECM as a complex with heparan sulphate. The heparanase of metastatic cells can do just that. Here again the cancer cells have learned how to imitate - at the wrong time, the wrong place and to the wrong extent - a natural activity (angiogenesis) for their own purposes.

Vlodavsky is now considering a new German-Israeli project. He would very much like to work again with his old German scientific colleague, Schirrmacher. However, their research emphases over the last eight years have drifted somewhat apart. Still, "Cooperate with someone else?" asks the modest Israeli scientist. He hesitates and then says, "The chemistry must be right, otherwise I cannot work."

Loss of Control

How viral infections can induce the transformation of cells: Project Ca 50

In Project Ca 50 two closely cooperating research groups examined how viral infections can sometimes induce the transformation of normal cells into cancer cells. Project Ca 50 has been marked both by particularly successful science and particularly close friendship

“Whatever I needed, I knew that I could ask Rolf and he would get it for me, no matter from where”, Mordechai Aboud remarked. Professor Rolf Flügel, a virologist, is Head of the DKFZ Division of Retroviral Gene Expression, and Mordechai Aboud is a Professor at the Ben-Gurion University of the Negev in Beer Sheva.

Generally BMBF-MOS researchers previously knew each other from scientific conferences or via common colleagues, before they applied for a joint project. However, Aboud had “never heard anything” about Flügel when he started, in 1991, looking for a research partner. He simply looked through the DKFZ’s most recent Scientific Report for a biologist whose research work corresponded to his own proposed investigation. Aboud sent his project proposal to Flügel who immediately “had good feelings” about it. He replied right away to Aboud, who then was spending his “summer vacation” working at the University of California in Los Angeles (UCLA) School of Medicine.

The joint research project submitted by the two virologists was accepted and funded for three years. Harald zur Hausen, Chairman and Scientific Member of the DKFZ Management Board estimates that ”about 15 per cent of all cancer diseases in the world can be traced to viral infections”. Viruses differ from their bacterial counterparts in that they multiply only within living cells. However, only a fraction of the persons infected with a tumor-causing virus ever develop cancer, and that often only decades after their initial infection. The Israeli-German research team was interested in learning what contributing factors are required to produce virus-induced cancer, and how such co-factors function. These co-factors may include carcinogenic chemicals, radiation or special genetic elements.

Research Collegues and friends: the virologists Rolf Flügel (second from left) of the Deutsches Krebsforschungszentrum and Mordechai Aboud of the Ben-Gurion-University of the Negev (second from right)

Aboud wanted to find out how a certain leukemia virus (HTLV-I) could interfere with the genetic mechanisms of the infected cells in a way that upset their growth control. HTLV-I, human T-cell leukemia virus type-I, appears mostly in Japan, West Africa and the Caribbean. Flügel, on the other hand, was studying the Spuma virus whose effects on human health and carcinogenesis is still largely unclear. Both types of viruses are retroviruses. That is, they carry their genetic information in RNA molecules. Once they get into a cell, these viruses convert their genetic information into DNA molecules, which are inserted directly into the genome of the host cell. Thenceforth, the host cell persistently carries these viral genes in addition to its own.

The victim notices nothing out of the ordinary until these dormant “provirus” genes are somehow activated. These viral DNA messages are then transcribed into messenger-RNA molecules which are, in turn, translated into viral protein molecules. Soon the virus begins to exploit the cells’ genetic and metabolic resources for its own purposes. More and more viral proteins and viruses are made and the infection spreads to neighboring cells.

Substances which damage the cellular DNA (desoxyribonucleic acid) are known also to induce the activation of the dormant “provirus.” The AIDS virus (HIV), another retrovirus, acts in this manner. Knowing the stimuli and signal pathways which “wake up” dormant leukemia viruses (and perhaps other retroviruses) might permit blocking

the further development of the disease at its onset. Most of the infected individuals would remain free of any symptoms, but they would still have to take care not to transfer the virus to others. HTLV-I, the subject of Aboud's study, resembles the AIDS virus in that it can be transmitted through sexual relations, blood transfusions or from a mother to her embryo.

Thanks to his cooperative project, Aboud was able to use the established expertise of Flügel's laboratory in his experiments. The Heidelberg group gave Aboud a genetic construct, which included both the LTR regulatory segment of the virus and the CAT reporter-gene. Aboud introduced the construct into healthy, virus-free cells, which he then exposed to a DNA-damaging chemical (carcinogen), 3-methylcholanthrene. This carcinogen was found to damage the cellular DNA and to activate LTR-directed expression of the CAT gene. The latter can easily be measured in the cells.

The scientists largely attribute the transformation of the blood cells caused by their leukemia virus to the Tax-protein, which is the virus' most important activator product. This protein not only switches on the viral genes, via the LTR segment, it also activates a number of host cell genes whose encoded proteins, such as interleukin-2 and GM-CSF, are involved in the regulation of cellular replication. However, the researchers question where the Tax-protein came from, since the Tax-protein is not produced so long as the provirus remains in its inactive dormant state. Aboud showed that Tax was not necessary for the initial activation step. Even in cells which did not contain Tax, he noted a remarkable stimulation of CAT activity by 3-methylcholanthrene. This carcinogen, then, seems to activate the expression of the viral genes by a different mechanism, one which does not involve Tax-protein.

Nirit Mor-Vaknin, Aboud's doctoral student, studied which genetic segments in the viral genome influence this effect. Molecular biologists can identify which DNA segments are critical for a given function by selectively eliminating them one after the other and seeing when the desired activity is affected. Mor-Vaknin learned how to produce such deletion mutants from Flügel's collaborator, Dr. Martin Löchelt, in Heidelberg. Löchelt, in turn, benefited from the experiences of the Israeli colleagues with Tax-protein in his studies of how the Spuma virus is activated.

Spuma virus activation involves a protein called Bel-1. Löchelt found a new Bel-1 binding site, besides the one known to exist in the viral LTR. It is located within the viral env gene. With this he discovered a previously unknown regulatory structure in retroviruses, an internal promoter.

A central role in virus replication is played by a protein complex encoded in the viral gene called pol. Flügel's doctoral student, Donat Kögel, who worked with Aboud in Beer Sheva for a few weeks in 1994, was the first to detect the pol proteins in virus-infected cells. The antibodies produced by Kögel specifically recognize the individual protein products of the pol-gene and are in much demand by his colleagues who are also investigating the pathogenic potential of the Spuma virus.

Not only did the professional capabilities of the two experienced senior researchers, Rolf Flügel and Mordechai Aboud, complement each other nicely, the two also became close friends. That was equally true of their collaborators. The German investigators considers it "an honor that Mordechai always stays with us at our home," and the Israeli cell biologist would "not even consider looking for a hotel".

The collaboration has resulted in eleven scientific publications, nine of which are joint publications. The other important success of the project, building one more small bridge between the nations cannot, however, be expressed in numbers. Rolf Flügel and Mordechai Aboud, who have already planned their next three years of joint research, "profit each day" from their cooperation. And in saying so, they refer to far more than just the scientific part of it.

Failure of the Guardian

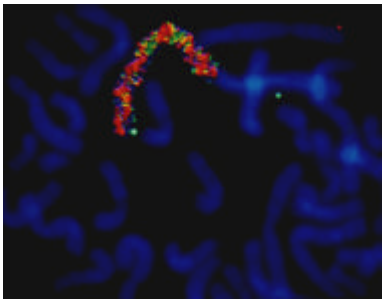
Project Ca 51: How the tumor suppressing effects of the p53 protein are eliminated in some neuroblastoma patients

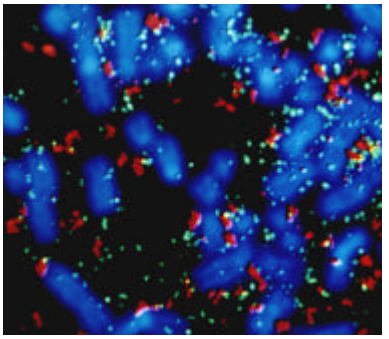
At the cutting-edge of current molecular-biological research, Project Ca 51 has enlarged our understanding of the cancer-suppressing effect of the p53 gene and resulted in a better picture of the most frequent solid cancer in young children, neuroblastoma. The outcome of the project may be one more element in eventually developing a more effective cancer therapy

In 1993 the prestigious scientific journal Science selected the p53 protein as their “molecule of the year.” The tremendous interest of researchers in this protein, named after its molecular weight of 53 kilodaltons, is based on its decisive role in preventing cancer (suppressing tumors) when functional and in allowing the formation of malignant tumors when impaired. The DNA sequences that encode the structural instructions for producing protein p53 are defective (mutated) in many cancer patients. For example, one finds p53 mutations (“errors”) in more than seventy percent of all colon tumor patients, half of all lung tumor patients, and in thirty to forty percent of all breast tumor patients. In some forms of cancer, however, although biologists find almost no defects in the p53 gene, the protective effect of p53 protein is blocked. One such tumor is the neuroblastoma, a nerve cell tumor which occurs mainly in small children. In Germany about 150 persons develop neuroblastomas every year, making them the most frequent solid tumor in children.

Professor Manfred Schwab, Head of the DKFZ Division of Cytogenetics, has studied the genetic specifics of neuroblastomas for more than 15 years. Under the DKFZ-MOS-Program in Cancer Research he joined forces with p53 expert, Dr. Moshe Oren of the Weizmann Institute of Science, whom he had met while working in the U.S. in the eighties. Successfully completed in 1994, their project (Ca 51) set out to discover how the tumor suppressing effects of p53 protein are eliminated in at least some neuroblastoma patients. This knowledge could one day increase the efficiency of therapy.

While working in the U.S. in the Eighties, Schwab demonstrated that in neuroblastomas a particular





Abnormal gene amplifications in tumor cells were detected with DNA fragments which were labeled with fluorescent dye

oncogene (N-*myc*) can be multiplied or amplified, between ten and a hundred times. The presence of multiple gene copies was correlated with a poor clinical prognosis, and today worldwide children positive for tumors with amplification are subjected to more sophisticated therapies. In his DKFZ-MOS project with Oren, Schwab used “reverse chromosomal in situ hybridization” to search for further genetic changes in this nerve cell cancer.

First he and Dr. Raffaela Corvi isolated, in their laboratory in Heidelberg, the genetic material (DNA) from neuroblastoma cells grown in culture flasks. They then used special biological reagents (restriction endonucleases) to cut the extracted DNA molecules into small fragments which were then bound to fluorescent (light-emitting) pigments. The DNA fragments were then mixed with the normal DNA readily obtained from normal blood cells. The DNA molecules, all double helices, were unwound in solution into two complementary strands. Under such conditions, the DNA fragments which were labeled with fluorescent dye became attached to their mirror image counterparts. Wherever the DNA of the cancer cells has replicated itself into multiple copies, more fluorescently labeled fragments will bind and that part of the chromosome will emit more light.

Raffaela Corvi noticed such a brightly lit amplification on chromosome 12 in three neuroblastoma cell lines and in one tissue sample freshly isolated from a neuroblastoma tumor. Comparison with a map of known genes identified the glowing site as the location of the cancer gene *mdm2*. It has been known since 1992 that multiple copies of this onco-

gene can appear in tumors of the connective tissues (sarcomas). Schwab found *mdm2* gene amplification in the neuroblastoma lines only when the N-*myc* gene was also amplified.

With mdm2-specific antibodies put at their disposal by Moshe Oren, the Heidelberg team showed the Mdm2 protein is produced excessively in neuroblastoma cells. How does this over-production of Mdm2 affect carcinogenesis? Mdm2 protein is known to form complexes with p53 protein. Using antibodies which bind both Mdm2 and p53 proteins (co-immunoprecipitation techniques), Schwab and his collaborators proved that there were also such complexes in nerve cell cancers.

Moshe Oren showed that the *mdm2* gene is itself a target of the p53 protein. The Israeli molecular biologist discovered a previously unknown regulatory segment within the *mdm2* gene (an internal promoter) to which p53 attaches itself. This interaction activates the *mdm2* gene and eventually results in production of Mdm2 protein.

Manfred Schwab notes that "in molecular biology much depends on the credible interpretation of the results." Oren, his Israeli partner and a recognized p53 expert, has now developed a model in which "the activation of the *mdm2* gene serves, via the p53 protein, as a negative feedback loop which terminates the p53 signal." This is important, because there must exist mechanisms not only for switching on signals in the cell, but also for switching them off once no longer required. The finely balanced growth control directed by p53 is only upset when, due to *mdm2* amplification, there is too much Mdm2 in the cell. However, the Mdm2 protein is not only sometimes harmful, it also is vital. "Knock-out" mice, whose *mdm2* gene has been artificially silenced, die as tiny embryos because, Oren presumes, the unrestricted activity of p53 drives the cells to suicide.

The p53 protein controls two complementary protective pathways. When DNA is damaged by radiation or chemicals, the p53 protein stops cell replication until repair enzymes can repair the damage. If the damage is so extensive that repair is impossible, p53 initiates the cell's suicide, a process known as programmed cell death or apoptosis. Similar mechanisms are activated in severe sunburn, when layers of skin cells die and peel off. If, however, a severely damaged cell were to survive, its genetic defects might derail the cell's normal, carefully balanced growth control mechanisms, and become cancerous. That is why the inactivation of p53 proteins (e.g., by certain viral proteins) so often has fatal consequences, as in human cervical cancer.

Oren also wondered why there is usually no functional p53 protein in most neuroblastoma cell-lines, even when the p53 gene is undamaged, a question he has been pursuing using Schwab's neuroblastoma cell lines. The Israeli group hypothesized that something may keep the p53 protein in the cytoplasm where it is produced, preventing it from reaching the DNA in the cell nucleus where it is needed. They found this indeed to be the case in neuroblastomas with *mdm2* gene amplification, although these are only a small fraction of all neuroblastomas.

Oren's findings may have clinical significance. If it were possible to remove the p53 "blockade" before radiation therapy, then p53 could enter the nucleus of tumor cells and there, given the great DNA damage deliberately inflicted by the radiation treatment, it could initiate apoptosis and speed the death of the targeted tumor cells. A similar approach has been used in treating testicular cancer, using cell differentiation-promoting substances to activate p53 before radiation therapy. Oren, the p53 specialists and Schwab, the neuroblastoma specialist, are now considering starting a new joint project to examine this hypothesis in the more complicated case of neuroblastoma cell lines.

The Roots

Cancer Research - Worldwide Challenge for Biomedicine

As different as their clinical appearance can be, all cancers have in common that they will eventually prove fatal - if not subjected to therapy. In industrialized countries all over the world, with increasing prevalence, cancer is the second most common cause of death after cardio-vascular diseases. Research on cancer diseases, aiming at their prevention or at successful therapy, is given high priority in the public health policy of all civilized nations. In this difficult area, biomedical research is particularly dependent on outstanding scientific discoveries - milestones of scientific knowledge. German scientists, including many of Jewish descent, and Israeli scientists have taken an active part in these achievements.

The progress of knowledge in cancer research was and still is tightly connected with contemporary innovations in methodological experimental approaches within biomedical research. The resultant new scientific knowledge finds immediate use for the alleviation of the patients.

In the following text, only some key references will be cited [bracketed]. Their complete citations may be found in the Appendix of the brochure under ”Selected References”.

Cancerogenesis - Classical Paradigms

In about the middle of the last century, numerous histopathological investigations on tissue material from cancer patients led the German pathologist, R. Virchow, to conclude that chronic inflammation might be the common denominator of cancero-genesis (”Reiztheorie”) [Virchow 1858]. Virchow postulated, in contrast to quite different contem-porary propositions, that cancer generally devolves from predamaged cells which yield neoplasms of unlimited proliferation. This classical paradigm of Cancer Etiology - Cellular pathology (see box) - indicated at first that - over and above the medical point of view - scientific understanding of the generation of cancer must be a problem of cell biology. It is in this direction which basic research on cancer diseases had to move in order to recognize with Goethe’s Dr. Faustus ”was die Welt im Innersten zusammenhält” (the force that binds all Nature’s energies).

Careful observations on workers afflicted with can-cer - mainly by clinicians, such as P. Pott (1775), R. von Volkmann (1875), L. Rehn (1895) and others - showed that soot, coal tar or aniline were occupa-tional causes of cancer of the skin or of the urinary bladder - chemical cancer risk factors. Soon after the introduction of X-rays into diagnostic medicine, knowledge on chemical cancer risk factors had to be extended by the first known, physical cancer risk factor: occupational exposure over the years to this otherwise useful irradiation induced in medical employees or medical doctors the so-called ”X-ray carcinoma” [Halberstädter 1923]. At about the same time, the American pathologist F. P. Rous dis-covered a filterable factor in chicken that caused sarcoma in healthy animals [Rous 1911]. This was the first biologically-induced cancer risk factor, later identified as a tumor virus (Rous sarcoma virus). For this discovery, Rous was awarded the Nobel Prize in 1966 (together with C.B. Huggins, for his discovery of hormone dependant tumors). The discovery of many more chemical, physical and biological factors in the human environment increasing the risk of cancer, led to the paradigm of the Environmental etiology of cancerogenesis (see box).

After a first, somewhat problematic, experimental generation of squamous cell carcinoma in the forestomach of the rat [Fibiger 1912], Japanese investigators unequivocally achieved experimental cancerogenesis in the rabbit ear using coal tar [K. Yamagiwa and K. Ichikawa 1914]. Fibiger was awarded the Nobel Prize in 1926 for the first experimental generation of cancer.

Paradigms of Cancer Etiology

Cellular pathology
Environmental etiology of cancerogenesis

Paradigms of Cell Biology

Chromosome mutation
Somatic gene mutation
Plasmagene mutation

Soon, it became possible to elicit experimentally typical cancers by exposure to environmental risk factors in nearly all multicellular animal species and in nearly all of their tissues or organs - from mammals to insects. Through these milestones of cancer research (after the unintentional occupa-tional exposure of people), experimental

cancerogenesis in animal models became available. They provided an appropriate means of investigating scientific questions on the causes of cancer diseases of the organism.

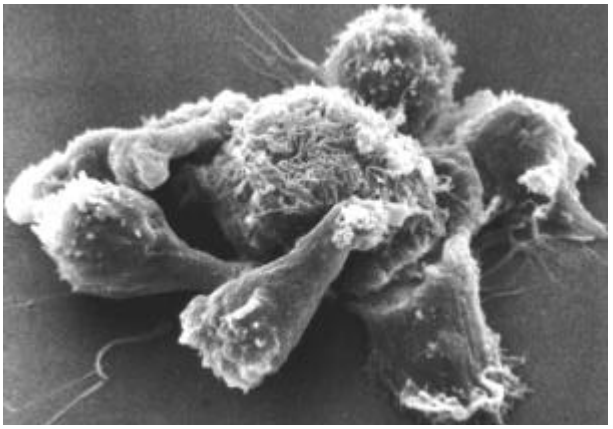
The spectrum of contemporary experimental methods in biology, biochemistry and toxicology and their application to problems of cancerogenesis, was steadily extended and deepened in the first half of the century. At its beginning, simple cell biological observations, stimulated by the previous detection of the Mendelian laws, led T. Boveri (1914) and K.H. Bauer [Bauer 1928], and later A. Graffi (1939) and C.D. Darlington (1944), to three somewhat different paradigms of cancerogenesis (see box). These early paradigms had to remain speculative for decades, since biology and biochemistry had no experimental approaches or methods availabe until recently to test their molecular nature at the cellular and subcellular level.

Paradigms of Biochemistry

Impairment of cellular respiration
Convergence of cytoplasmatic enzyme pattern
Deletion of enzymes or regulatory proteins

Much earlier methods available were the analytical enzymologic methods of biochemistry, e.g., measurement of cellular respiration in Ehrlich ascites tumor cells, for which O. Warburg (1926) was awarded the Nobel Prize. These results may be summarized in the paradigm of Impairment of cellular respiration, a first biochemical paradigm of cancerogenesis (see box). Following Warburg, the biochemical-enzymologic techniques were extended to numerous organs and tissues. These techniques were, in turn, effectively supplemented and advanced by the totally new possibility of radioactive labeling of biomolecules. The combined techniques led, especially given the results achieved by Greenstein (1956), V.R. Potter (1964) and J.A. and E.C. Miller (1947), to further milestones of knowledge regarding the causes of cancer. They may be expressed in the paradigms of Convergence of cytoplasmatic enzyme pattern as well as of Deletion of enzymes or regulatory proteins (see box).

After years of pure empirism, the biochemical differences detected between normal cells and the corresponding tumor cells provided chemo- and irradiation therapy of cancer diseases for the first time with an apparently rational basis. In analogy



Immunocells attack a cancer cell

to the concept of therapy of infections with antibiotics (e.g. sulfonamides), the final goal was to selectively kill the tumor cells in neoplasms and to save the normal cells. However, up to that point, this goal could be achieved only with limited success. The main reason for the limited results was the crucial fact that the biochemical differences between tumor and normal cells mostly are only quantitative in nature, rather than qualitative, unlike the differences between bacterial and mammalian cells. This view was pointed out by Potter [1964] in the introduction to his symposium lecture where he notes: ”Recent developments in the field of biochemistry have given us all renewed hope that definitive chemical differences between tumor cells and the normal cells from which they are derived will soon be discovered.” The biochemical differences then detected have therefore to be considered rather as secondary consequences of the yet unknown primary cellular causes of cancerogenesis. Due to a lack of qualitative differences between cancer cells and normal cells, trials of cancer immunotherapies also remained unsuccessful for a long time.

The dissatisfying results of cancer therapies initiated to date focused attention on the idea of preventing the generation of cancer diseases by prophylactic measures, i.e., to let the evil not even develop (cancer prevention). The importance of this approach may be illustrated by reports, that e.g., in the USA presently more than 75 - 80 per cent of all deadly cancer cases may be ascribed to cancer risk factors of the environment and hence, in principle, are preventable.

Paradigms of Toxicology

Solitary cancerogens (tumor initiators) display in target tissues no threshold doses of cancerogenic efficacy. Their essential primary lesions in target cells are irreversible

Cancerogenesis is a pathogenic multiple-stage process which may be caused by one or more risk factors (cancerogens)

Conditional cancerogens (tumor promoters) display in initiated target tissues threshold doses for cancerogenic efficacy. Their essential primary lesions in initiated target cells are reversible

To develop prophylactic measures of cancer prevention (cancer prophylaxis), toxicologic research on the cause of cancerogenesis is required. A first milestone was recognition of the quantitative relations between dose, time and efficacy for chronic exposure to chemical cancerogens. Successful initial investigations of this kind were performed by M.R. Bryan and M.B. Shimkin (1943) as well as by H. Druckrey and his coworkers [Druckrey and Küpfmüller 1948]. They established the principle of "complete cancerogens", the new paradigm of - according to present terminology [Arcos et al. 1995, Appel et al. 1990] solitary cancerogens (or tumor initiators) (see box). The organotropy of efficacy of solitary cancerogens was unravelled by extended investigations, especially of cancerogenic nitroso compounds.

The quantitative relationships between dose/time and efficacy established for solitary cancerogens are typical for risk factors causing essentially irreversible primary lesions in target cells. In view of the paradigm of somatic gene mutation, it was H. Druckrey who first termed cancer risk factors of this type "genotoxic" [Druckrey 1972 - quoted in Ramel 1990]. Following Druckrey, the hereditary persistance of genotoxic primary lesions by solitary cancerogens was later impressively confirmed and extended by perinatal cancerogenesis as well as by multigeneration cancerogenesis. B.N. Ames coined the somewhat provocative slogan "Carcinogens are mutagens". He referred to the short term mutagenicity assays in bacteria he had proposed as surrogates of chronic exposure, for rapid detection of the solitary cancerogenic activity of environmental materials (Ames-tests). In careful reinvestigations of the assay within the framework of the U.S. National Toxicology Program, this slogan was found to be, at least for bacterial testing, by no means strictly valid. Later on, in molecular biologic investigations of the true target cells for solitary cancerogens, a refinement of this slogan to "Solitary cancerogens are mutagens" was stringently proven.

As a further milestone, the so-called "Berenblum experiment" must be mentioned. This experiment, designed by Isaac Berenblum after the precedents M.J. Shear (1938) and J.F. Mottram (1944), was stimulated by the "Reiztheorie" (Virchow). It provided the first hints that the process of cancerogenesis may proceed in stages [Berenblum and Shubik 1947, Berenblum 1974]. Today this is almost taken for granted; the stages may be caused by one or more factors. This may be summarized as the paradigm Cancerogenesis is a pathogenic multiple stage process which may be caused by one or more risk factors (cancerogens) (see box).

However, what precisely, is the design of the Berenblum experiment? Berenblum succeeded in generating tumors using the dorsal skin of mice as a model, following a particularly elegant protocol with the skin irritant croton oil comprising two operationally defined stages. He called these stages "tumor initiation" and "tumor promotion". Often the Berenblum experiment is referred to as the initiation/promotion protocol (I/P-protocol) in mouse skin or as the Two-Stage Model of Cancerogenesis. The two stages may be properly extended by a third stage as well, called "tumor progression", to make up a Three-Stage Model for the entire process of Cancerogenesis. With Croton oil, a tumor promoting risk of cancer was detected for the first time; this may be usefully designated a "conditional cancerogen".

At about the same time, A. Butenandt and coworkers - soon after his detection of the estrogenic hormones - recognised the "conditionally cancerogenic" activity of these non-irritant, proliferation-stimulating hormones in the mammary glands of mice. In convincing experiments, it was shown simultaneously that solitary cancerogenic efficacy of hormones per se does not exist [Butenandt 1950].

The existence of cancer amplifying or augmenting, but per se non-cancerogenic risk factors - analo-

gous to Croton oil or estrogens - had long been suspected, especially from clinical experience in human patients [Bauer 1963]. Nevertheless, a number of researchers tended to assign to Croton oil as well as to estrogenic hormones, a (weak) solitary cancerogenic activity. This fundamental dissent nourished a decade-long scientific controversy on the existence or non-existence of tumor promoters (or conditional cancerogens) i.e., risk factors of cancer with another (alternative) quality of cancerogenic activity, as compared with that of tumor initiators (or solitary cancerogens).

The scientific controversy stimulated Berenblum and other researchers to try to characterize the true active principles or the risk factors - the tumor promoters - of Croton oil. This was finally accomplished by E. Hecker and his co-workers in Heidelberg, as well as almost simultaneously and independently by B. van Duuren and co-workers in New York. The tumor promoters of Croton oil were discovered to be esters of the novel tetracyclic diterpene phorbol. Their prototype, 12-O-tetradecanoylphorbol-13-acetate (TPA or sometimes also PMA), is known worldwide today as an important tool for biochemical cell research [Hecker 1976, 1985].

To decide the fundamental problem above, the I/P-protocol was highly standardized in NMRI-mice to obtain quantitative toxicologic data for cancerogenic activity by tumor promoters which could be validated statistically. The quantitative dose/time/efficacy relationships for TPA displayed - in contrast to tumor initiators (solitary cancerogens) - well-defined threshold doses. Below the threshold doses, no tumor-promoting activity was observed [Hecker and Rippmann 1990]. Analogous dose/time/efficacy-relationships were established for many other related diterpene ester tumor promoters as well as, later on, for indolalkaloid and polyacetate type tumor promoters. These findings provided - in today's terminology [Arcos et al. 1995, Appel et al. 1990] - the new paradigm of Conditional cancerogens (or tumor promotors) (see box).

Quantitative dose/time/efficacy relationships with threshold doses are characteristic for chronic exposure to risk factors that cause essentially reversible, i.e., non-genotoxic primary lesions in their target cells. In contrast to those of tumor initiators they are supposedly of an epigenetic nature: indeed, TPA and other diterpene esters are not covalently bound, e.g., to proteins of mouse skin. Also, qualitative structure activity relations of TPA and phorbol derivatives indicated strongly that receptors may be present in their target tissue [Hecker 1978].Today, for the most diverse tissues and organs (liver, bladder, intestine, esophagus, etc.), numerous cancerogens are known for which the quality of tumor promoters may be ascribed (non-genotoxic cancerogens). Conditional cancerogens (or tumor promoters) therefore represent another, i.e., a second category of defined cancer risk factors of the environment. They differ toxicologically and fundamentally from solitary cancerogens by their quantitative dose/time/efficacy relationships as well as, most probably, by their cellular primary lesions. They represent alternative potentials of cancer risk. It was proposed, therefore, to classify them as first- and second-order risk factors of cancer, respectively [Hecker 1985, 1990].

Experimental cancer research in Israel was started upon the arrival of Leonid Doljanski, 1935

Measures of cancer prevention may be based upon two key consequences of the classification of cancer risk factors: (1) Exposure to solitary cancerogens (tumor initiators) - first-order risk factors of cancer - has to be avoided strictly as regards doses, length of time, and number (or frequency) of exposure. (2) Exposure to conditional cancerogens (tumor promoters) - second-order risk factors of cancer - has to be restricted as regards doses and times of exposure. The extent of restriction depends upon

the particular circumstances of exposure.

Both of these key consequences taken together allow for a more differentiated and balanced assessment of the cancer risk by environmental cancerogens of whatever origin and nature as required, e.g., for risk/benefit considerations. They will contribute to providing more appropriate measures of cancer prevention, e.g., by national bodies responsible for environmental health and safety [Hecker 1990]. What remains, however, is to outline adequate methods for detection, identification and classification of a putative cancer risk by environmental materials, especially as regards the non-genotoxic conditional cancerogens (see below).

The paradigms of toxicology, covering chemical (and physical) risk factors of cancer, began to emerge while biological cancer risk factors in the environment - especially viruses - were still denied as causes of human cancer by most pathologists and clinicians: clinically they have never become apparent as infectious diseases [see, for example, Bauer 1963]. A first breakthrough regarding the causative role of oncogenic viruses as cancer risk factors in man was the discovery of numerous DNA- and RNA-tumor viruses and their possibile cellular latency [zur Hausen 1985 (see below)].

Cancer Research in Germany

Traditionally, research on cancer was originally carried out in Germany by surgeons and pathologists at the universities. In addition, some of the Kaiser-Wilhelm-Institutes founded at the beginning of the century (today known as Max-Planck-Institutes) were concerned experimentally with problems of cancer research. Moreover, in four places in Germany, special divisions or institutes for cancer research were established. Besides financial difficulties, they also had to struggle with considerable resistance from their medical colleagues. The latter considered institutions of this kind mostly as competition of medical faculties in universities concerned with treatment and therapy of cancer patients. A further line of development for cancer-related research in Germany came from organizations dedicated to ”cancer research and the fight against cancer”. As early as the end of the last century, initiatives of this kind led medical doctors and scientists to demand targeted research in the fight against cancer. In 1900 these activities led to the foundation of the ”Comité für Krebsforschung”, an early predecessor of today’s Deutsche Krebsgesellschaft e.V.. In 1903, the Comité founded and published the oldest journal of cancer research in the world: ”Zeitschrift für Krebsforschung”. Today - after several publishing and scientific metamorphoses - it appears as Journal of Cancer Research and Clinical Oncology at the Springer-Verlag, Heidelberg and serves as an organ of the Deutsche Krebsgesellschaft e.V..

The development of scientific knowledge concerning cancer, and the growing complexity of corresponding biomedical research at about the beginning of the second half of this century, made it more and more imperative for the classical biomedicinal specialities to cooperate in problems of research on cancer. Thus, after re-establishment of the research organizations in Germany around 1950, the creation of a new type of cancer research establishment, - a multidisciplinary cancer research center - was proposed. Within such a center, basic and applied biomedical research should be centralized (”under one roof”-principle) at the national level.

A first attempt by the Max-Planck-Society (MPG) to establish such a center as one of its institutes failed in 1956. The initiative was then taken over by the Deutsche Forschungsgemeinschaft. At that time the Society used to assemble most of Germany’s know-how in cancer research in its so-called ”Hinterzartener Kreis”, chaired by Nobel laureate, Professor Adolf Butenandt (president and thereafter honorary president of the Max-Planck-Society 1960-1972). The ”Kreis” met in a workshop once a year to discuss both biomedical and clinical problems in cancer research. Butenandt and other members of the circle, e.g., Nobel laureate Professor Richard Kuhn, Director of the Max-Planck-Institute for Medical research in Heidelberg, persuaded the Senate of the University of Heidelberg to support and promote the concept of a national cancer center located in Heidelberg. Of the members of the circle, Professor Karl Heinrich Bauer, emeritus and former Surgeon and Director of the Surgery Department of the University of Heidelberg, was strongly in favor of the principle of assembling classical disciplines of biomedicine ”under one roof” in a National Cancer Research Center. He strongly supported as a surgical clinician and medical doctor the development of a German cancer research center in Heidelberg, particularly in view of his ”Theory of Somatic Gene Mutation of Neoplasms” [Bauer 1928].

As a result of long-lasting and difficult negotiations with the local State of Baden-Württemberg, the Deutsches Krebsforschungszentrum (DKFZ) was finally founded and opened in Heidelberg in 1964. It was led by a Directorium composed of the directors of the seven founding institutes. Five of the classical institutes (Biochemistry; Experimental Pathology; Information, Documentation and Statistics; Nuclear Medicine; Toxicology) were situated in provisional buildings on the campus of the University of Heidelberg, at the periphery of the city. Two further institutes (Experimental Cancer Research and Virus Research) remained in University buildings close to the center of the city of Heidelberg.

Science at the DKFZ was led internally by the Directorium and a Scientific Council. It was coordinated beyond the limits of the specialities of the classical institutes by six multidisciplinary research areas pursuing cancer-related topics. In this way the internal cooperation of the divisions in the classical institutes was interlinked by a kind of ”matrix of research”. In September 1972, all seven Institutes moved into the large, jointly-planned (at that time new) building occupied today. This ensemble was soon complemented by an eighth Institute of Immunology.

Financially and administratively the DKFZ was maintained at first by the government of the local State of Baden-Württemberg and the Federal Government of Germany, as an establishment of the so-called ”Königsteiner Staatsabkommens”. In 1976 its status was changed and it become known as a “Großforschungseinrichtung” (National Research Center) and public foundation. Its ”Satzung” (Constitution) designates the Management Board (Stiftungsvorstand) as the leading body and the Scientific Council (Wissenschaftlicher Rat) as a counselling organ. The supervising body for the Federal Ministry of Education and Research (BMBF) is the Board of Trustees (Kuratorium).

Through the initiative of the Deutsches Krebsforschungszentrum, important German university hospitals, and the Deutsche Krebsgesellschaft, so-called Oncological (clinical) Centers have been established within the Federal states since the middle of the Seventies. The Tumor Center Heidelberg/ Mannheim, for example, was founded with the local involvement of the Deutsches Krebsforschungszentrum.

The Directorium (Chairman: Professor Klaus Munk) and the Scientific Council (Chairman: Professor Erich Hecker) started to develop programs for international cooperation, the cooperation program with Israel being the first. It was established in 1976 by an agreement with the National Council for Research and Development (NCRD) of the State of Israel in Jerusalem (see page 65).

On the appointment of the virologist Professor Harald zur Hausen as Chairman and Scientific Member of the Stiftungsvorstand in 1983, a new Institute of Applied Tumor Virology was added as an important extension of the Deutsches Krebsforschungszentrum.

In this constellation of nine institutes the Deutsches Krebsforschungszentrum celebrated in 1989 the 25th Anniversary of its founding (see Current Cancer Research, 1989; Interdisciplinary Science Reviews 1989).

Today the scenario of ”research on and fight against cancer” in the Federal Republic of Germany comprises the Deutsches Krebsforschungszentrum as the national center of basic research on the cancer problem, the oncological centers of the universities as institutes for clinical cancer research and treatment of cancer patients, and the German Cancer Society as the society for this scientific speciality. This scenario is complemented by a number of cancer-related scientific journals. A critical review of the current state of cancer research in Germany was given recently [zur Hausen 1998].

Cancer Research in Israel - The Early Years
The establishment of the first units for clinical oncology and for experimental cancer research in Israel (Palestine) was directly linked to the exodus of Jewish physicians and scientists from Germany in the early thirties.

The first department for oncology and radiotherapy in Israel (Palestine) was founded in 1933 at the Hadassah Hospital in Jerusalem. The first director of this department was Professor Ludwig Halberstädter, who introduced in Jerusalem the techniques of radiotherapy with radioactive radium needles. Prior to his emigration from Germany, Halberstädter was the Director of the Department of Radiotherapy at the Cancer Research Institute in Berlin-Dahlem. He was renowned for the introduction of methods for radiotherapy with well-defined

doses of radium and for the discovery of the trachoma virus corpuscles. Two of Halberstädter's colleagues in Berlin, Drs. Tigendreich and Simons, emigrated from Germany to Palestine in 1934 and 1938 respectively, and established a cancer radiotherapy unit in Tel Aviv.

Experimental cancer research in Israel was started upon the arrival of Professor Leonid Doljanski, a renowned German scientist in this field. Doljanski had received his M.D. degree from the University of Berlin. After two years of work at the Pasteur Institute in Paris, he returned to work in Berlin. He was employed by the Kaiser Wilhelm Institute for Biology in Berlin-Dahlem from 1930 until the ascent of the Nazi regime forced him to leave Germany abruptly in 1934. For a year (1934 -1935), he worked in Copenhagen, Denmark with Dr. Albert Fisher and arrived in Israel in 1935. Doljanski was a pioneer in the field of tissue culture. Using advanced methods of tissue culture, he carried out outstanding studies on the identification of growth and differentiation factors. His work on the effect of the Rous virus on the in vitro transformation of chicken fibroblasts was the first to demonstrate the direct oncogenic capacity of the Rous virus in vitro.

Doljanski was responsible for the opening of the Cancer Research Laboratories of the Hebrew University of Jerusalem in 1935. As stated in a contemporary publication from this laboratory complex, these facilities were "the first cancer research laboratories in the Near and Middle East".

In August 1940, the Cancer Research Laboratories were transferred to the Nathan Ratnoff Building of the Hebrew University of Jerusalem on Mount Scopus. The Cancer Research Laboratories consisted of three departments: The Department of Experimental Pathology, which was headed by Doljanski; the Department of Radiology, headed by Halberstädter; and the Department of Cancer Chemistry, headed by Professor Yeshaya Leibowitz. Like the heads of the other two units for cancer research at the Hebrew University, Professor Leibowitz had a distinguished academic career in Germany before coming to Palestine. He received his M.D. degree in Berlin in 1924. Among his academic appointments in Germany, he was an assistant at the Kaiser Wilhelm Institute for Biochemistry in Berlin-Dahlem and at the Department of Physiological Chemistry at the University of Cologne.

Under the scientific leadership of Leonid Doljanski, the Department of Experimental Pathology became a very active center for cancer research, attracting many scientists who themselves later became prominent Israeli scientists. The high esteem in which Doljanski was held by his colleagues was evident from his appointment as Dean-elect of the Medical School of the Hebrew University which was about to be opened.

The activity of the Department of Experimental Pathology came to an abrupt halt in April 1948 when a convoy of University scientists and Hadassah Hospital personnel, who were on their way to Mount Scopus, was brutally attacked by Arab snipers, killing 77 persons. Among those killed was Leonid Doljanski, who at the time was only 48 years old.

It took some time till the surviving scientists, who had worked under the guidance of Doljanski, regrouped and reestablished the Department of Experimental Medicine at the "Bible House". Those who participated in this effort included Professor Annah Rosin, a prominent pathologist trained by Professor Ludwig Aschoff in Freiburg; Dr. Esther Taennenbaum, a master of tissue culture techniques; and Dr. Leah Bloch-Frankental, an experienced biochemist. Dr. Mary Pikovski carried out pioneering work on mammary cancer in mice and on immunological tolerance. Among her students were Michael Schlesinger (see page 99) and Isaac Witz, both of whom carried out studies on the immune system in relation to cancer [Schlesinger 1972, Witz 1996]. Fanny Doljanski-Ettinger, the daughter of Leonid Doljanski who had worked with him in the laboratory, devoted her research to studies of the dynamics of the cell membrane. For some time Dr. Emanuel Margoliash was Chairman of the Department. In 1957 Professor Jack Gross from Montreal, Canada, was appointed as Head of the Department, that was then called the Department of Experimental Medicine and Cancer Research.

An important development in the history of cancer research in Israel proved to be the immigration of Isaac Berenblum from England. In 1955 he became professor and Head of the Department of Experimental Biology at the Weizmann Institute of Science in Rehovot. Berenblum gained international renown for his clear formulation of the stages of carcinogenesis, with particular emphasis on the

process of co-carcinogenesis or tumor promotion. He attracted to his new department such scientists as Professor Leo Sachs, who characterized the factors regulating the differentiation of neutrophils and monocytes leading to the discovery of interleukin-6. Among the prominent co-workers of Berenblum was Professor Nathan Trainin who discovered and characterized the thymic humoral factor (THF), which proved to be an important regulator of the immune system. Professor Michael Feldmann, who initially worked in Berenblum's department, carried out important studies on immunogenetics of tumors and on tumor metastasis. Professor Nechama Haran-Ghera became an expert on leukemogenesis.

Among the scientists who developed biotechnological aspects of cancer research was Professor Michel Revel who carried out pioneering studies on interferons and initiated their large scale production and clinical application for the treatment of cancer patients [Revel 1995].

Over the years laboratories for cancer research were established in all the Universities in Israel. Many of the new driving forces and heads of departments were themselves students of scientists who paved the road in this research endeavor and had taken part in development of the early paradigms. Most of the new generation of Israeli scientists benefited from post-doctoral training abroad, in leading laboratories for cancer research and molecular biology. Today, hundreds of bright young scientists are engaged in cancer research in the various institutes and hospitals all over Israel. They represent an enormous potential of biomedical knowledge available for the urgently necessary multidisciplinary cooperation in cancer research.

Numerous centers of medical oncology for the treatment and care of cancer patients were established over the years throughout Israel. The Israel Cancer Association, a nationwide voluntary organization, plays a vital role in supporting medical treatment and psycho-social help for cancer patients, in furnishing information about cancer to the public, and in providing seed money for cancer research. One of the presidents of the Association was Nathan Trainin.The high esteem the international community holds for cancer research and the fight against cancer in Israel was indicated recently (1998) by the election for president of the International Union Against Cancer (UICC, Geneva) of the well-esteemed clinical oncologist from Haifa, Professor Eliezer Robinson. Robinson and Trainin have been, Revel, Schlesinger and Witz are members of the Scientific Program Committee (see Appendix, page 108).

A Centennial Dogma Brake off

From about the beginning of the second half of this century, enormous methodological progress in biochemistry and biology began to develop. This considerably extended the, so far, mostly descriptive results and knowledge of cell biology and precipitated a fundamentally new, molecular biological view of cell functions. The importance of these new methods and of the resultant knowledge - milestones of cell biology - is already obvious from the fact that the leading researchers involved were almost always awarded the Nobel Prize, mostly in physiology or medicine. Within the framework of this article, even of these milestones, only those may be briefly mentioned that are considered most important for understanding the molecular biological developments regarding the cancer problem.

Revelation of the molecular structure of DNA as a double helix based upon refined X-ray structure analyses (Watson-Crick-Model of DNA) was a first milestone (Nobel Prize, Watson, Crick, Wilkins 1962). Of crucial importance for cancer research was the surprising discovery that the genetic information leading to transformation of cells by tumor viruses is present in latent form even in normal cells, well before a viral infection has taken place. In other words, the genome of a normal cell contains in certain nucleotide sequences "cellular oncogenes" (c-onc), often also called "protooncogenes". Large portions of their nucleotide sequences are homologous to nucleotide sequences of tumor viruses (v-onc) which were identified independently (Varmus and Bishop, Nobel Prize 1989). Moreover, the genome of the normal cell contains so-called tumor suppressor genes which may suppress uncontrolled multiplication of cells.

From manifold new knowledge on the genome of the cell and its functions, it follows that the centennial dogma of classical biology is obsolete: for almost 100 years - from the discovery of the laws of inheritance by Gregor Mendel (1865) to the identification of the structure and function of DNA (1953) - the genome of the cell was almost unanimously considered as a purely static, even rigid, structure.

In reality, the genome of the cell was discovered in molecular biological terms, to be an unexpectedly dynamic DNA-structure which, however, is precisely controlled functionally.

Abandoning the central dogma of classical biology, however, is only one of the consequences resulting from contemporary molecular biological research. It has rapidly become obvious that it is not enough to decipher the genome of the cell alone. To understand the complex network of physiological functions in the totality of a cell, the proteins of the cell as an entity of their own, the so-called proteome, has to be recorded and analyzed as well. This has become possible through current methodological progress. Only by analyses of the proteome under well-defined conditions, can it be clarified which regions of the genome are expressed in what quantity and how the resultant gene products are modified post-translationally.

Molecular biological knowledge has contributed critically to a deeper understanding of cancerogenesis at the cellular and subcellular level and to our knowledge of the molecular nature of pathologic deviations of the norm. It has precipitated new developments in cancer prevention as well as in cancer diagnostics and cancer therapy. Thus, the possibility of preparing so-called monoclonal antibodies allowed the updating and improvement of classical histopathologic tumor diagnostics in terms of a modern immunohistopathology [Franke 1993]. The latter allows an enormous increase of sensitivity in recognizing neoplastically altered cells in human cancer tissues.

Change of paradigms is due
The toxilogical paradigm of Solitary cancerogens (or tumor initiators) in itself implied genotoxic primary lesions by these cancer risk factors in the target cells, yet it could not prove it. This situation remained unchanged until the application of current methods of research employing molecular biology, gene technology and bioinformatics. These new methods revealed that the impact of chemical tumor initiators (or solitary cancerogens) resulted in persistant mutations in protooncogenes or tumor suppressor genes. These find a measureable expression in altered sequences of nucleotides in the damaged genes. This means a change of the corresponding paradigms to molecular toxicology: Tumor initiators (solitary cancerogens) cause as primary molecular lesions persistant mutations in the genome of target cells (Proto-oncogenes or tumor suppressor genes (see box)).

Paradigms of Molecular Toxicology

Tumor initiators (solitary cancerogens) cause as primary molecular lesions persistant mutations in the genome of target cells

Tumor promoters (conditional cancerogens) cause as primary molecular lesions in the proteome of target cells non-covalent interactions with elements of growth control

In the initiation stage of the I/P-protocol (Model: Berenblum experiment), for example, the tumor initiator DMBA causes a mutation of the H-ras protooncogene in Codon 61 of keratinocytes of mouse skin as primary molecular lesion: The normal base sequence CAA of the protooncogene is converted to the base sequence CTA. Single or multiple persistant mutations in protooncogenes or tumor suppressor genes by tumor initiators (or solitary cancerogens) are known today for numerous target cells. The mutant genes express altered proteins as gene products which interfere in an irregular manner with para- and/or autocrine regulation networks of the cell.

The toxilogical paradigm of Conditional cancerogens (or tumor promoters) implied non-genotoxic primary lesions of epigenetic nature in the target cell by these cancer risk factors, but without final proof. The application of modern methods has revealed - for the promoters so far investigated - that they interact in the proteome with diverse receptors and/or regulatory proteins of growth control in a non-covalent, e.g., agonist type, manner. In this way, they activate the functions of these receptor and/or regulatory proteins of the target cell in a non-physiological manner. This finding calls for a further change of toxilogical paradigm to: Tumor promoters (conditional cancerogens) cause as primary molecular lesions in the proteome of target cells non-covalent interaction with elements of growth control (receptors, regulatory proteins, see box)).

In keratinocytes of mouse skin in the promotion stage of the I/P-protocol (Model: Berenblum experiment), for example, promoters of the TPA-activity type interact by an agonist-type binding to membrane bound or cytoplasmatic protein kinases C (PKC). This activates the phosphorylation capability

of the receptors. In the same model promoters of the alternative okadaic acid-activity type bind to certain cytoplasmic or membrane-bound protein phosphatases as receptors. The agonist-type binding of the promotors inhibits the dephosphorylation capability of the receptors [Fujiki and Suganuma 1993].

The new paradigms of Molecular toxicology postulated refer essentially to investigations in the mouse skin model of the I/P-protocol. They will have to be challenged and perhaps modified in target cells of other known models of the I/P-protocol (liver, bladder, intestine, esophagus, etc.).

In the case of estrogens as tumor promoters, it is assumed that they interact with initiated cells, containing mutations in hormonally-regulated protooncogenes and/or tumor suppressor genes, or else an otherwise altered genomic architecture. Initiated cells of this kind may be stimulated by the cytoplasmic estrogen receptor complex to non-physiological (potentially neoplastic) growth.

The new paradigms of Molecular toxicology demonstrate that tumor initiators (or solitary cancerogens) cause relatively uniform, irreversible, primary lesions in the genome of the target cell. The primary lesions of the tumor promoters (or conditional cancerogens) investigated so far are seen to occur in in the proteome of initiated cells. Depending on the kind of target cell (skin, liver, etc.), they may affect diverse reversible primary lesions. They may occur in receptors or other regulatory proteins involved in para- and/or autocrine regulatory networks of growth control.

With respect to cancer prevention, detailed molecular knowledge of the different mechanisms of action of solitary and conditional cancerogens may be used with great benefit: this knowledge gives valuable hints for specific short-term assays to be used as surrogates for chronic exposure. In this way environmental materials may be tested in a simple and inexpensive way for solitary or conditionally cancerogenic activity, and categorized regarding their potential of cancer risk. Thus, expensive, and ethically doubtful, chronic whole animal experiments may be deleted. In this way detection of ”genotoxic” and/or non-genotoxic cancer risk factors in the human environment may be accelerated considerably and at low cost. In addition, knowledge of the molecular mechanisms of action of tumor promoters (conditional cancerogens) may be useful for devising new approaches to chemoprevention of cancerogenesis or to chemotherapy of cancer, e.g., by use of inhibitors of the stage of tumor promotion.

Cancer Treatment and Molecular Medicine

In the investigation of cancerogenesis, the clarification of associated cancer risk factors received primary attention. A possible predisposition of the organism itself, usually called the ”host”, is considered as a constant, yet by no means a neglegible, parameter. It was recognized early in cancerogenesis research that cancer may occur in experimental animals also spontaneously, i.e., without obvious or targeted impact of environmental risk factors. In different strains of one and the same experimental animal (e.g. mice) occurence of spontaneous tumors may vary considerably. Clinical experience with cancer patients often has indicated that also human beings may be genetically disposed to certain cancer diseases. This is subsumed under a so-called “family history” of the disease [see Bauer 1963]. Current molecular biologic investigations indicate that predisposed experimental animals or individuals contain damaged genes in the genome of their cells, i.e., mutations in protooncogenes or in suppressor genes. Just one single mutation in the entire genome of human beings may suffice, i.e., a single base exchange in the DNA, as is the case in retinoblastoma, a rare inheritable cancer disease of the eyes. But the genome may also be damaged by a multiplicity of mutations, e.g., in case of certain inheritable intestinal cancers.

Theoretically, genomic lesions achieved by exposure to cancer risk factors, or inborn, may be eliminated by so-called gene therapy. One may try, for example, to replace the defective or damaged part of the genome by an intact one.

Other approaches of molecular medicine try to replace deleted functions in cancer cells and to bring them back - re-differentiate them - to some kind of normal condition [Sachs 1986]. In cultures of certain cells, this approach is successful, using, for example, particular phorbol esters to induce re-differentiation, e.g., in hamster cells or in cells of erthyroleukemia (HL-60 cells) . It is presently under active study for therapy of human cancer. A number of other approaches to cancer therapy are still in the experimental stage, for example, trials to induce the suicide program of apoptosis [Krammer]

in cancer cells and so elimi-nate them. Other therapeutic concepts are attempts to make cancer cells recognizable to the immune defense system of the patient [active specific immunotherapy (ASI), adoptive immunotherapy (ADI); Schirrmacher 1995]. Vaccination, for example against pigmented skin cancer (melanoma) or against early cancer stages of the cervix uteri, is also presently being developed [zur Hausen 1996].

Presently much hope rests on "Molecular Medicine". Altogether it may be foreseen that the enormous complexity of cellular events at the molecular level will make it increasingly necessary to investigate individually each of the more than 100 cancer diseases known in man and to develop new approaches for cancer prevention and cancer therapy down to the level of molecular details. This means, for research on cancer in the future, that a marked and far reaching specialization in research programs is required together with increasing efforts for their financing [Puchta 1998].

New Organizational Structures

The dramatic developments in molecular biology, gene technology, and bioinformatics and the resultant changes of paradigms in cancer research have had their impact on the organizational structures of cancer research in the Deutsches Krebsforschungszentrum as well as in the partner organizations in Israel: in each case purposeful reorganizations were the reaction.

Soon after the 25th Anniversary of the Deutsches Krebsforschungszentrum (1989) the classical "founding institutes" were given up as units of research and replaced by divisions [zur Hausen 1992]. The former integral research areas were replaced by novel research programs. The topics of the research program are related directly to basic biomedical problems of cancer diseases, and are extended where appropriate by so-called "clinical cooperation units" (see page 66, 98). All research programs at the DKFZ are of a multidisciplinary nature; in their frame different divisions or project groups work together, each of them contributing the appropriate specific methods and research approaches of various biomedical disciplines to reach the goal of the common research program (see page 66). Moreover, the divisions contribute in a specific way to quick conversion of the results of basic research into practical measures for cancer prevention and/or for cancer therapy.

Priority Topics announced in 1998

1. Molecular Aspects of Apoptosis in the Control of Malignancies

2. New Insights into Specific Genomic Rearrangements Prevailing in Neoplastic Cells

3. Novel Approaches to Cancer Therapy Based on Specific Molecular Targets

The reorganization of the research activities in the Deutsches Krebsforschungszentrum and in the research establishments in Israel naturally is reflected also in the joint Cooperation Program. This may best be seen from the research topics of the seven new cooperative projects started - shortly after the 20 year anniversary - in Summer 1996 and again in another seven new cooperative projects started in January 1998. The new design of research is also reflected in the three new Priority Topics of the Call for Proposals announced in Summer 1998 (see box above).

At a global level much has been achieved in recognizing, with regard to cancer diseases, "was die Welt im Innersten zusammenhält" (the force that binds all Nature's energies). To this end also the joint research in the first twenty years of the cooperation of the Deutsches Krebsforschungszentrum with Israeli research establishments has distinctly contributed. Very much more remains to be done in the future to control cancer diseases, i.e., to be more successful in their prevention and in their therapy - to the benefit of mankind.

Bridges of Communication

(No) Partner like every other: What German and Israeli scientists think about the cooperation

The German-Israeli Cooperative Program in Cancer Research has, over the last 20 years, not only produced outstanding scientific results; it has also promoted many strong personal friendships.

At first the cooperation between the Deutsches Krebsforschungszentrum (DKFZ) and the National Council for Research and Development (NCRD), the precursor of the Israeli Ministry of Science (MOS) had only served basic national purposes. Since the mid-Seventies, the Israelis had been increasingly looking abroad for the funds they needed for important research projects. On their side, the German cancer research scientists were interested in making contact with outstanding scientists in Israel. Although this program blossomed into much more than a dry, formal partnership, considerable personal hurdles and suspicion first had to be overcome on both sides. The following illustrative vignettes cast light on the evolving personal relationships and attitudes that have characterized this program.

Michael Schlesinger of the Hebrew University (HU) in Jerusalem was one of the first participants of the new Cooperation Program. Schlesinger is a well-known immunologist. His breakthroughs on the characterization of immune cells earned him a lead article in the prestigious international publication Cancer Research. In 1976, the HU Authority for Research and Development, an office which assists HU scientists to raise research funds, had publicized the availability of German research funds and partners. Schlesinger had a special interest in collaboration with German scientists. He had been born in 1932 in the Rheinland-Palatinate town of Worms, about 100 kilometers southwest of Frankfurt. His parents fled to Palestine shortly after the National Socialists came to power.

For many years after the Holocaust, Schlesinger did not want to have anything to do with Germany, either scientifically or personally. This was typical of many Israeli scientists of his generation. As he put it, “There was always the question of: What were this person’s activities during World War II?” His attitude changed only when, more than 20 years after the War, a visiting deputy from the Rheinland-Palatinate Legislative Assembly invited him to visit Worms, his birthplace. Schlesinger recalls that “these were the first German visitors who knew my family.”

His mother had come from an old Worms family called Loeb. She had studied medicine at the Universities of Freiburg and Heidelberg and had practiced medicine in Worms, specializing in dermatology. Schlesinger’s father had been decorated with the Iron Cross during World War I; and his grandmother had been a German poet. German culture had remained the most important culture in Schlesinger’s family even after they moved to the Middle East. Although after the war the German language was scorned in Israel, Schlesinger studied it as an adolescent with a teacher who was also a refugee from Germany.

For his “outstanding contributions to the success of the German-Israeli Program” the Meyenburg Lecture was awarded to Michael Schlesinger (left). In the middle: Hermine Hecker, right: Erich Hecker, DKFZ-Coordinator of the program, second row: Nurit Topaz, MOS (left) and Max Burger, member of the Program Committee

Although Schlesinger originally “really did not want to travel to Worms”, his talks with his visitors and their blameless past convinced him to accept their invitation. Ever since then he returns as often as he can to his birthplace, where one day an old lady even greeted him as the “son of Mrs. Loeb”.

Michael Schlesinger finds that the hesitant friendliness of Israelis towards older Germans and their unequivocal cordiality towards younger Germans “remains for many of my German friends quite surprising.” Their doubt about their reception led most to be “very quiet about the fact that they were German.” Volker Schirrmacher, a DKFZ immunologist, remembers his own doubts during his first visit to Israel in 1972. He was surprised when a

vendor at a newsstand answered him in German, when he asked him in English for a German news magazine. He was even more surprised when his partner in Project Ca 24, Israel Vlodavsky (Hadassah University Hospital), invited him to spend Passover with him at the kibbutz where his sister and mother live. Most of Schirrmacher's projects are now "with Israeli friends." These include six projects within the BMBF-MOS cooperative framework.

Michael Schlesinger is a long-time member of the Cancer Program Committee and, in 1997 the Deutsches Krebsforschungszentrum and the Wilhelm Maria Meyenburg-Stiftung awarded a Meyenburg-Lecture to him "for his outstanding contributions to the success of the German-Israeli Program". On another occasion Schlesinger invited Erich Hecker, DKFZ Coordinator for the Collaboration, to spend Passover with his family, joining his children who were flying in from the USA for this important Jewish family celebration.

A German journalist visiting Israel for the first time was soon introduced to Israeli hospitality. She was initially surprised when her guide urged her to end an appointment not later than 1:30 p.m.; but understood once her guide mentioned a family gathering. Later she was dumbfounded when she realized that the rush was designed to allow her to participate in the family's festivities.

As a biochemist, Erich Hecker knows from experience that scientific cooperation brings people together, even if their political opinions differ. "That is of no importance; one leaves one's opinions outside." Scientists even leave their native languages "outside," usually conversing in English in their laboratories. That is how, in 1959, Otto Hahn, Wolfgang Gentner and Feodor Lynen (respectively a chemist, physicist and biochemist) initiated such fruitful German-Jewish scientific relations with their Israeli colleagues at the invitation of the Weizmann Institute.

Still, Michael Schlesinger, who was Vice President of the Hebrew University (HU) from 1977 to 1982, notes that the situation is not always easy on both sides. "There are academicians in the [HU] Faculty of Humanities who still have problems with Germany." Schlesinger also remembers how, in the Seventies, the Israeli head of a large HU project publishing a special edition of the Bible had refused

Michael Schlesinger's hometown Worms in the beginning thirties

to accept the funding which Germany had put at his disposal Conversely, an archaeologist at a German university was afraid that cooperation with Israel could prejudice his coveted rights to carry out digs in Iran and Iraq. "Slowly, slowly there was progress."

For the new generation, scientific cooperation between Israel and Germany is no longer out of the ordinary. Schlesinger notes it makes no difference to his children whether they travel to England, France or Germany. Still, however, there remains some sensitivity and ignorance on both sides, and Israelis with German roots have a particular responsibility to build bridges of understanding between Germany and Israel.

Friendship cannot be prescribed and, in the case of collaboration between Israeli and German cancer researchers, it has blossomed on its own. Even though this cooperative program is devoted to a highly specialized scientific goal, progress in scientific understanding is almost always linked with progress in interpersonal understanding and friendship.

The Future

Multinational Research on Cancer

The German view of the cooperation program with Israel

Cancer research has many faces as there are causes for tumor growth, as there are characteristics by which tumor cells differ from their healthy counterparts, and as there are strategies available to tumor cells to escape the immune defense of the organism. Nowadays even a good-sized scientific center can meet only in part the immense challenges of multidisciplinary cancer research. Its own competence with respect to handling problems of methodological multiplicity and the capability of rapid evaluation of new achievements for their potential for rapid transfer into clinical practice has to be selectively enhanced by extramural scientific cooperations with competent partners. The research program of the Deutsches Krebsforschungszentrum thus maintains a total of 800 cooperations with scientists in Germany and abroad.

At the national level the Deutsches Krebsforschungszentrum is a member of the Association for Clinical-Biomedical Reserach (Verbund Klinisch-Biomedizinischer Forschung) in which National Research Centers have joined for closer cooperation. Mainly clinical aspects of cancer diseases are covered by multidisciplinary cooperation with oncologic centres in Germany, above all the neighbouring Tumor Center of the University Heidelberg/ Mannheim. New clinical cooperation units, interactive structures between academic and non-academic clinical research, considerably extend the clinical orientation of the Deutsches Krebsforschungszentrum. Moreover, the Deutsches Krebsforschungszentrum is part of the BioRegio-Association. Under the auspices of the German Human Genome Project, a Center for Resources was established at the Deutsches Krebsforschungszentrum (and in the Max-Planck Institute for Molecular Genetics in Berlin) and operates as central service unit.

At the international level, working contracts exist with about 300 universities and non-academic research establishments. Besides renowned Israeli research establishments, the Institute Nationale de la Santé de la Recherche Medical (INSERM) in Paris, France, and the National Cancer Institute in Bethesda, USA may be mentioned. In addition the Deutsches Krebsforschungszentrum houses two ”WHO-Collaboration Centers” (for Nuclear Medicine and for Human Papilloma Viruses), which include a multitude of national and international contacts.

In the interplay of all these scientific cooperations, the formalized scientific program with Israel is especially valuable for the Krebsforschungszentrum. On the one hand there is scientific excellence of the roughly 60 cooperation projects up to 1996 and of the more than 500 scientific publications arising from these (complete bibliography may be found in the Supplement to this Brochure). On the other hand there is the fact that gradually - despite initial reservations by the Israeli investigators - in the course of the research program many personal relations and friendships have developed giving the impression that bridging the deep gaps of the past is successfully being accomplished (see also page 99).

Through a reorganisation of its scientific infrastructure - from the rigid structures of classical institutes to cancer-oriented flexible research programs - the Center has also gained flexibility with regard to the future of the special cooperation program with Israel.

The present eight Research Programs (see page 66, 98) indicate an almost complete shift of the Center’s research program towards molecular-biologically oriented cancer research. Particularly in these areas collaboration with experienced research partners can be most important. For example, given the increasingly closer interconnections of genome research, protein analysis and function determinations, both Israelis and Germans will profit considerably from mutual competent partnerships. And for the organ-related investigations of cancer diseases planned by the Deutsches Krebsforschungszentrum, closer relations with several clinical-oncologic centers in Israel are advisable.

In the future as in the past, the scientific cooperation with Israel, sixty years after the Holocaust, cannot be based just on cost-benefit considerations. The existing, stimulating cooperation with the Israeli scientists of today was built not only on scientific excellence but also on the enormous personal involvement and special effort of many people (see Acknowledgements). Yet, at this point it can exist also under normal conditions of competition as it has developed to become the standard for today’s international science.

The German-Israeli cooperation program in cancer research is recognized as a highly esteemed model of scientific cooperation. This was confirmed by an international evaluation of the first twenty years of the program in 1997 [Mann 1998]. It was initiated by the national Ministries concerned in Bonn (BMBF) and Jerusalem (MOS) and led by the International Agency for Research on Cancer (IARC, Lyon, France) of the World Health Organization (WHO). The evaluating committee has recommended full continuation of the program, if possible with extension of its scope (see box opposite).

In the future, despite limited financial resources, the Stiftungsvorstand of the Deutsches Krebsforschungszentrum has decided actively to develop the cooperation with Israel: from mid-year of 1996 and up to January 1, 1998 altogether 14 new cooperation projects have already started work. Moreover, the projects approved for the Priority Topics of the next phase of the cooperation, advertized in summer 1998 (see box page 98), will start operation on July 1, 1999.

The International Evaluation

"1. The Evaluation Committee unanimously concludes that this is a very successful framework of cooperation that over the past twenty years has grown not only in volume and extent of funding, but also in the quality of scientific output. The programme carries a wide range of important topics in cancer research, ranging from basic aspects of malignant transformation to clinical aspects and epidemiology. The members of the committee therefore strongly recommend to continue and, whenever possible, expand this programme.
2. The committee recommends to maintain the current pattern of a three-year funding period and a new round of applications every eighteen months. This allows sufficiently to adapt to new research topics without increa sing the administrative workload associated with applications on a yearly basis. However, the committee recommends that in each round of applications a maximum of two projects should be considered for extension, based solely on scientific excellence.
3. It is recommended to maintain the system of priority topics but to formulate them in a sufficiently broad manner to allow any excellent group working in basic cancer research to apply.
4. The selection committee should see that in addition to established laboratories, young investigators have a fair chance of being funded.
5. The committee was impressed by the efficient administrative handling of this programme and does not see a need to change the administrative or financial procedures established over the past two decades."

Professor Bernhard Fleckenstein
Erlangen, January 6, 1997

Professor Paul Kleihues
Lyon, January 6, 1997

Professor Leo Sachs
Rehovot, January 6, 1997

DKFZ-MOS Cooperation: The Israeli Perspective

The Israeli scientists and administrators responsible for the DKFZ-MOS research program foresee continuing, mutually beneficial cooperation, based upon a firm foundation of past success. Through the years, the DKFZ-MOS program has become an important avenue for the advancement of cutting-edge cancer research. The program has made important contributions to the strengthening of Israel's scientific infrastructure in centrally important areas, including cancer molecular genetics and cell biology, tumor virology, cancer immunology, carcinogenesis and metastasis.

In coming years, the Program should focus its resources on topics which are likely to lead the way in the investigation of the causes of cancer, its prevention and cure. Among the priority areas particularly appropriate for inclusion in the DKFZ-MOS program are control and regulation of gene expression, tumor vaccines and cytokine-mediated cancer therapy.

Research on cancer is not, of course, a matter of purely scientific-professional importance. It is also an expression of the common moral concern to alleviate suffering and promote the general welfare of mankind. Thus, there is a special significance to cooperation between German and Israeli scientists in a field such as cancer research; and it is particularly gratifying to note that results of DKFZ-MOS projects have already found expression in cancer public health measures and clinical practice in Israel, Germany and elsewhere. To guarantee the contribution of Israeli and German scientist' joint endeavors to the improvement of health standards, greater emphasis should be given to the dissemination and application of the research findings.

Finally, through the years, the supportive attitude of the German partner organisations and researchers has found expression not only on the bilateral plane, but also in their willingness to help open the doors of European research networks for Israeli scientists. This has been true in the specific field of cancer research and, more recently, in the broader context of Israel's accession to the European Union's Framework Program for Research and Technological Development. As the process of European unification advances and Israel's integration into the European Framework Program is strengthened, it is important that the sides make a conscious effort to exploit their strong bilateral links in cancer research as the basis for complementary multilateral activities.

German-Israeli bilateral links in the study of cancer also have an important role to play as a foundation for scientific cooperation aimed at confirming and strengthening the ties of peace between Israel and her Arab neighbors. German scientists, as respected colleagues and friends of both Israeli and Arab researchers, can play an important mediating role in projects on research topics of both Middle East regional and general scientific significance.

Acknowledgements

Scientists who participated in cooperation projects (see Appendix, page 112), or those who are involved presently, as well as the Scientific Program Committee (present and former members, see Appendix, page 108) deserve sincere gratitude for their active involvement before and during realization of the projects.

Gratitude is due to the Federal Ministry of Education and Research, the Israeli Ministry of Science, the Management Board of the Deutsches Krebsforschungszentrum and especially to those who have contributed and still do so invaluably, ”behind the scenes”, to the success of the Cooperation Program.

In alphabetical order:

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Working for the program: Elfriede Mang, Yair Degani, Elfriede Egenlauf and Erich Hecker (from left to right)

Appendix

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Members of the Program Committee

Membership of the DKFZ/MOS Program Committee for Cooperation in Cancer Research from 1976 to the Present, in Alphabetical Order

Israeli Members (including MOS-Coordinator):

Prof. Dr. Jacob Bar-Tana,
Department of Medical Biochemistry, the Hebrew University - Hadassah Medical School, Jerusalem: 1979 - 1980

Dr. Yair Degani,
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Prof. Dr. Zvi Fuks,
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Prof. Dr. Nechama Haran-Ghera,
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Prof. Dr. Iafa Keydar,
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Prof. Dr. Michel Revel,
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Prof. Dr. Avraham Yaniv,
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European Members (including DKFZ-Coordinator):

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Prof. Dr. Bernhard Fleckenstein,
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Prof. Dr. Dres. h.c. Harald zur Hausen,
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Prof. Dr. Erich Hecker,
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Prof. Dr. Rolf Knippers,
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Prof. Dr. H.G. Rammensee,
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Prof. Dr. Erwin Rüde,
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Temporary Procedure
To Generate Common Projects

Cooperation Program in Cancer Research between Deutsches Krebsforschungszentum (DKFZ) Heidelberg and Ministry of Science (MOS)

Version 1996

1. General

Within the time period covered by the contract between DKFZ(BMFT, now BMBF) and NCRD (National Council for Research and Development, now MOS) a "DKFZ-MOS Joint Program in Cancer Research" will be materialized in "Common Projects" which fit in with the Research Program of the DKFZ. The joint program will be governed by a "Program Committee" (see contract by DKFZ and NCRD, now MOS). Each common project comprises at least one "Subproject" from each of the partner organizations, the DKFZ and the MOS. Common projects will be defined by a descriptive title covering its principal research topic, supplemented by subtitles to characterize the cooperating individual subprojects. Whenever feasible, for administrative convenience, the cooperation is performed in "Phases of Cooperation", each comprising several common projects.

2. Generation of Common Projects and Program Coordination

To generate common projects, Israeli and German subproject proposals are called for by the MOS and the DKFZ, respectively. Within the amount of funds forecasted to be available by the DKFZ, the financial ceiling and deadlines for subproject proposals will be defined by the Program Committee (for detailed mechanism, see below). Coordination of subproject proposals to form proposed common projects is assisted by the partner organizations through "Program Coordinators". Simultaneously they are members and may be Vice-Chairpersons of the Committee with a certain limitation in voting (see below). Presently the Program Coordinators are Dr. Yair Degani, MOS, and Professor Dr. Erich Hecker, DKFZ.

3. Raising of Subproject Proposals and their Matching to Form Proposed Common Projects

3.1 Call for cooperative subprojects: for any phase of the cooperation program, upon proposal by the DKFZ and after coordination with the MOS, the Program Committee will discuss and approve Priority Topics for common projects. On such topics calls for proposals of collaborative subprojects will be issued by the MOS and DKFZ within their respective scientific communities.

Whenever possible, partnerships should be arranged by direct communication and interaction between Israeli and DKFZ principal investigators prior to submission of fully written subproject proposals to their research organization. The rules according to which fully written subproject proposals are to be submitted are defined by the respective partner organization. Israeli grantees from previous phases of the cooperation program, but not DKFZ grantees, are excluded from participation for one phase (period of three years). Generally, in each phase of the cooperation program, a DKFZ grantee can have only one cooperative subproject. In extraordinary cases, after appropriate consideration by the DKFZ (e.g. capacity of DKFZ grantee involved) at the earliest possible stage of the procedure and as an exception, he may be approved by the committee to have two subprojects.

To identify potential partners the program coordinators may assist applicants from either partner organization. To do so the coordinators require the following preliminary materials (1-2 pages) at the earliest possible date relative to the closing date of the call:

1) Name and address (affiliation) of Israeli principal investigator
2) title of the subproject to be proposed
3) Short summary of the applicant's subproject proposal
4) specific aspects of the common research project for which the applicant is seeking a cooperating partner, including the expected contribution of the partner and the mode of cooperation envisaged.

If, for any given Israeli subproject proposal, a partner from within the DKFZ is not available, as notified by the DKFZ Coordinator on the basis of the

preliminary materials, the proposal may be rejected by the MOS after notifying the DKFZ. Alternatively, the Israeli applicant may search for a competent partner, preferably from the University of Heidelberg, but possibly also from another university in Germany. The eligibility as a potential partner of any specific German non-DKFZ scientist requires individual special approval by the DKFZ. To apply for it requires nomination of a "sponsor" from within the senior scientists of the DKFZ who, upon request by the Scientific Council and/or by the Management Board of the DKFZ, verbally presents the intended common project to these scientific bodies of the DKFZ. Such sponsor may or may not participate actively in the joint project by means of a subproject. Applications for the special approval by the DKFZ are to be submitted to its program coordinator by either the Israeli or the putative German subproject partner(s). Such applications must cover the following preliminary items and shall be received no later than 60 days prior to the closing date for submission of fully written proposals:

1) Names and addresses (affiliations) of the Israeli and the German applicants.
2) Title of the common project to be proposed, integrating the topics of the cooperating subprojects.
3) Titles of the Israeli and German subproject proposals.
4) Short summaries of each of the subproject proposals, indicating their mutual crosslinks to make them a true cooperation of the partners involved.

Decisions of the DKFZ regarding such applications will be made no later than 30 days prior to the closing date for submission of fully written proposals. If permission is granted by the DKFZ, the principal investigators submit fully written subproject proposals to the respective partner organization by the closing date of the call for fully written proposals.

3.2 Matching of subproject proposals is based upon exchange of lists between the partner organizations, covering subproject proposals by title and name of the principal investigator proposing the subproject. The exchange takes place no later than 14 days after the closing date of submission of fully written subproject applications.
3.3 Count down of proposals of common projects.

After the deadline for submission of fully written subproject applications, the MOS will select at most twice as many matched subprojects as can be financed. The MOS will provide to the DKFZ fully written proposals of matched subprojects including a financial plan and nomination of the title and partner of the matching DKFZ subproject. Confidential priority ratings (I high, II - less high) may be stated. This information shall be conveyed to the DKFZ for evaluation no later than three months before the next Program Committee Meeting. Once the MOS has submitted the fully written proposals to the DKFZ no other Israeli subproject proposals will be considered.

In turn, but no later than one month before the next Program Committee Meeting, the DKFZ will provide to the MOS fully written proposals of its subprojects, with nomination of the title and partner of the matching MOS subproject proposal.

Proposed subprojects, their matching and priority ratings are not binding for either partner organization. Decisions of the partner organizations on nomination of subprojects and ratings are to be kept confidential.

3.4 Evaluation of common projects by Program Committee. No later than two weeks prior to the next Program Committee Meeting the DKFZ will submit to the Program Committee the proposed common projects by common title, supplemented by the subtitles and the descriptions defining the subprojects. The Program Committee will evaluate the scientific merits of the subproject proposals submitted to the partner organizations as well as their matching to form proposed common projects.

4. Decision(s) on proposed common projects

In a first round, the Program Committee will discuss and evaluate all common projects proposed by the DKFZ/MOS.
In a second round, the Program Committee by simple majority vote of the members present, excepting both coordinators, will decide on approvals. For competitive evaluation the criteria 1-5 below, with or without formal rating, are to be applied:

1	Originality and scientific quality	0-1-2-3
2	Relevance to cancer	0-1-2-3
3	Probability of fruitful interactions	0-1-2

4	Reliability of methods proposed	0-1-2
5	Cost/Benefit ratios	0-1

Highest priority proposal(s) reach a total of 11 points from criteria 1-5. Zero at any single criterion means rejection of the entire subproject proposal. Subprojects rated identically may be subrated further according to any one or all of the following criteria:

I Preferably young Israeli or DKFZ investigators
II Preferably balanced geographic distribution of participating Israeli institutions
III Preferably diversification of the proposed subprojects within the priority topics advertised.

A proposed common project may be rejected either totally (all subprojects together) or partially (any of the component subprojects). In case of a partial rejection, the Program Committee may consider alternative proposals and suggestions by the partner organization.

All ratings of the Committee have to be kept strictly confidential.

5. Release of Decision on Common Projects

The decision of the Program Committee on approval of a proposed common project will be communicated in writing through each of the partner organizations to the applicants of the relevant subprojects as soon as possible. To give such information to the applicants, by either partner organization the standard text, as found in the Operational Appendix (p. 2) of this Procedure, must be used.

By now this Procedure and its Operational Appendix are based upon experience collected in 19 years of the DKFZ/MOS cooperation program. It is proposed herewith by the Program Committee to the partner organizations for exploratory implementation.

Dr. Y. Degani	Prof. Dr. E. Hecker
Program Coordinator MOS	Program Coordinator DKFZ

Projects Concluded

61 Projects were concluded in the first 20 years (Projects Ca 1 - Ca 62, 01.01.76 - 30.06.96)

The Projects are arranged according to their affiliation to Research Areas (RA). Mostly, but not necessarily, their affiliation to RA is identical with affiliation to one of the Research Programs of the Deutsches Krebsforschungszentrum

Cell Differentiation and Carcinogenesis

Ca 2
L. Sachs, Weizmann Inst.
W. Franke, DKFZ
Membrane organisation in leukemic cells - kinetics of formation and heterogeneity of surface membrane components and mosaics and its interference with membranotropic drugs
01.01.76 - 31.12.79

Ca 7
E. Shaaya,
E. Sekeris, DKFZ
Regulation of synthesis of HnRNA in epidermis cells of insects and its post transcriptional modification
01.01.76 - 31.12.79

Ca 22
B. Geiger, Weizmann Inst.
W. Franke, DKFZ
Biochemical and immunochemical characterization of type-specific intermediate filaments and their attachment sites in normal and in transformed cells
01.01.83 - 13.12.85

Ca 30
V. Rotter, Weizmann Inst.
V. Schirrmacher, DKFZ
P53 expression in tumor cells of different metastatic capacity
01.01.86 - 31.12.88

Ca 33
Y. Milner, Hebrew Univ
M. Hergenhahn (E. Hecker), DKFZ
The role of plasma membrane physical organization in control of human epidermal cells
01.01.86 - 31.12.88

Ca 36
B. Czernobilsky, Kaplan Hosp.
W. Franke, DKFZ
Intermediate filaments in germ cell tumors
01.07.87 - 30.06.90

Ca 46
A. Ben-Ze'ev, Weizmann Inst.
J. Kartenbeck (W. Franke), DKFZ
Regulation of synthesis of intermediate filament and desmosomal proteins in attached filament and desmosomal proteins in attached and unattached states of normal and transformed cells
01.01.91 - 31.12.93

Ca 47
Y. Shiloh, Tel-Aviv Univ.
A. Weith (M. Schwab), DKFZ
Amplification in human solid tumors: search for new oncogenes
01.07.90 - 30.06.93

Ca 49
B. Geiger, Weizmann, Inst.
M. Schmelz (W. Franke), DKFZ
Structure-function relationships in adhering cell junctions of normal and transformed cells
01.07.90 - 30.06.93

Ca 58
E. Keshet, Hebrew Univ. -
Hadassah Med. School
E. Spiess, DKFZ
Regulation of proteases and their respective inhibitors mediating cell invasivenes during angiogenesis and metastasis
01.07.93 - 30.06.96

Ca 61
V. Rotter, Weizmann Inst.
K.H. Richter (F. Marks), DKFZ
The involvement of tumor suppressor p53 in differentiation
01.07.93 - 30.06.96

Ca 62
B. Shilo, Weizmann Inst.
B. Mechler, DKFZ
Signalling pathways of Drosophila receptors and tumor suppressor gene products
01.07.93 - 30.06.96

Tumor Cell Regulation

Ca 5
F. Doljanski, Hebrew Univ.
V. Kinzel, DKFZ
Cell surface shedding in normal and neoplastic cells
01.01.77 - 31.12.80

Ca 17
R. Simantov, Weizmann Inst.
F. Marks, DKFZ
Biochemical dissection of early promotion specific and pleiotropic effects evoked by phorbol ester tumor promoters and related compounds
01.07.81 - 30.06.84

Ca 21
J. Kapitulnik, R. Koren, Hebrew Univ.
F. Kolar, N. Fusenig, DKFZ
Alteration of growth regulation in chemical carcinogenesis
01.07.82 - 30.06.85

Ca 25
S. Shaltiel, Weizmann Inst.
M. Gagelmann (V. Kinzel), DKFZ
Structure of cAMP-dependent kinases as bioregulatory enzymes
01.01.83 - 31.12.85

Ca 34
J. Schlessinger, Weizmann Inst.
V. Kinzel, F. Marks, DKFZ
The role of polypeptide growth factors in multistage tumorigenesis
01.01.86 - 31.12.88

Ca 37
I. Friedberg, Tel Aviv Univ.
D. Kübler (W. Pyerin), DKFZ
Role of cell surface-mediated utilization of extracellular nucleotides in normal and transformed cells
01.07.87 - 30.06.90

Ca 52
H. Degani, Y. Salomon, Weizmann Inst., W. Lehmann (W.E. Hull),DKFZ
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
01.01.92 - 31.12.94

Ca 53
S.A. Lamprecht, Ben-Gurion Univ.
P. Krieg (F. Marks), DKFZ
Transforming growth factor-beta in epithelial growth control, differentiation and neoplasia
01.01.92 - 31.12.94

Ca 54
M. Liscovitch, Weizmann Inst.
V. Kinzel, DKFZ
Role of phospholipase C and D in cell signaling and growth control
01.01.92 - 31.12.94

Ca 55
J. Bar-Tana, Hebrew Univ
D. Keppler, DKFZ
Cell signaling and growth control induced by amphipathic carboxylates - an unifying theory
01.01.92 - 31.12.94

Ca 56
I. Ginzburg, Weizmann Inst.
H. Ponstingl, DKFZ
Arrest of cell divsion in tumor cells by inducing expression of control proteins: (A) Cytoskeletal Tau MAP (Israel), (B) Mitotic Control Proteins (Germany)
01.07.93 - 30.06.96

Ca 59
A. Kimchi, Weizmann Inst.
N. Fusenig, DKFZ
Negative regulating growth factors and the significance of their abrogation in carcinogenesis
01.07.93 - 30.06.96

Cancer Risk Factors and Prevention

Ca 16
R. Ben-Ishai, Technion
H.W. Thielmann, DKFZ
A study of the mechanism of environmental carcinogenesis
01.01.80 - 31.12.82

Ca 20
M. Herzberg, Tel-Aviv Univ.
D. Werner, K. Munk, DKFZ
Nucleic acid binding activities and nucleolytic activities associated to the nuclear matrix in mammalian cells
01.07.82 - 30.06.85

Ca 40
J. Kark, Hebrew Univ
J. Wahrendorf, DKFZ
Biochemical predictors of 20 year cancer incidence in the Israeli civil servant cohort
01.01.89 - 31.12.91

Ca 45
P. Rozen, Ichilov Hosp.
H. Boeing (J. Wahrendorf), DKFZ
Dietary factors in the recurrence and progression of colorectal adenomas; A calcium intervention study
01.01.89 - 31.12.91

Diagnostics and Experimental Therapy

Ca 11
T. Mekori, E. Robinson, Haifa Technion
H. Kirchner, E. Storch, DKFZ
Mechanisms of immunosuppression in cancer patients and experimental models. The role of adjuvant radio-chemo- and immunotherapy
01.07.79 - 30.06.82

Ca 12
D. Sulitzeanu, Hadassah Med School
M. Zöller, S. Matzku, DKFZ
Identification and biological activity of antigens in immune complexes of patients with breast cancer
01.07.79 - 30.06.82

Ca 13
J. Treves, S. Biran, Hadassah Univ. Hosp.
W. Dröge, V. Schirrmacher, DKFZ
Specific adoptive immunotherapy of human and experimental tumors by lymphocytes sensitized in vitro against autologous tumor cells
01.07.79 - 30.06.82

Ca 23
U.Z. Littauer, I. Ginzburg, Weizmann Inst.
H. Ponstingl, DKFZ
Cytostatic binding sites in normal and corresponding tumor cells
01.01.83 - 31.12.85

Ca 51
M. Oren, Weizmann Inst.
R. Corvi (M. Schwab), DKFZ
Analysis of tumor suppressor genes in human cancers
01.01.92 - 31.12.94

Applied Tumor Virology

Ca 1
E. Winocour, Weizmann Inst.
G. Sauer, DKFZ
Integration of SV40 into the cellular genome
01.01.76 - 31.12.79

Ca 9
S. Lavi, E. Winocour, Weizmann Inst.
G. Sauer, DKFZ
Synergistic carcinogenic effects of viral and chemical agents and DNA mutagenesis in primates
01.07.79 - 30.06.82

Ca 10
J. Witz, Tel Aviv Univ.
K. Munk, DKFZ
Systemic and in-situ tumoral immunity in rats inoculated with Herpes-Simplex Virus (HSV) transformed cells and bearing metastasizing tumors
01.07.79 - 30.06.82

Ca 19
E. Canaani, Weizmann Inst.
T. Graf, DKFZ
Virus-mediated genetic rearrangements
01.07.82 - 30.06.85

Ca 26
A. Panet, Hebrew Univ.
H. Kirchner, H. Jacobsen, DKFZ
Inhibition by interferon of Herpes Simplex Virus or regulation of other viruses in murine cells
01.07.84 - 30.06.87

Ca 31
S. Mitrani-Rosenbaum, Hebrew. Univ.
L. Gissmann, DKFZ
Detection and characterization of human papilloma viruses in genital lesions from Israelian patients
01.01.86 - 31.12.88

Ca 32
S. Lavi, Tel-Aviv Univ.
J. Schlehofer (J. Rommelaere), DKFZ
The role of DNA-amplification in tumor initiation
01.01.86 - 31.12.88

Ca 35
H. Manor, Technion-Inst.
M. Pawlita (L. Gissmann), DKFZ
Carcinogen-induced replication and recombination of polyoma and lymphotropic papovavirus DNA
01.01.86 - 31.12.88

Ca 48
J. Tal, Ben-Gurion Univ.
J. Schlehofer (J. Rommelaere), DKFZ
Involvement of the NS genes in the antitumor activity of parvoviruses
01.07.90 - 30.06.93

Ca 50
M. Aboud, Ben-Gurion Univ.
M. Löchelt (R. Flügel), DKFZ
Tumorigenic cooperation between human retroviruses, oncogenes and other carcinogens
01.01.92 - 31.12.94

Ca 60
S. Lavi, Tel-Aviv Univ
R. Heilbronn, M.P.I. für Biochemie, München
J. Kleinschmidt (J. Rommelaere), DKFZ
Onco suppression by adeno-associated viruses
01.07.93 - 30.06.96

Tumor Immunology

Ca 3
M. Schlesinger, Hebrew Univ.
W. Dröge, DKFZ
Analysis of lymphocyte subpopulations with a combination of physical and serological techniques
01.01.77 - 31.12.80

Ca 4
R. Laskov, Hebrew Univ.
K. Eichmann, DKFZ
Control mechnisms of immunoglobulin synthesis in myeloma cells
01.01.77 - 31.12.80

Ca 8
J. Haimovich, Tel-Aviv Univ.
P. Krammer, DKFZ
Differentiation of normal and malignant T and B lymphocytes
01.07.79 - 30.06.82

Ca 14
E. Pick, Tel-Aviv Univ
D. Gemsa, H. Kirchner, DKFZ
Macrophage activation induction and effects on cell cooperation
01.10.79 - 30.09.82

Ca 15
D. Givol, P. Lonai, Weizmann Inst.
K. Eichmann, DKFZ
Expression of Immunoglobin variable region determinants on functionally defined T lymphocyte populations
01.10.79 - 30.09.82

Ca 18
S. Segal, E. Gorelik, Ben-Gurion Univ.
G. Hämmerling, V. Schirrmacher, DKFZ
The Immunobiology of tumor metastases
01.07.81 - 30.06.84

Ca 24
I. Vlodavsky, Hadassah Univ. Hosp.
V. Schirrmacher, DKFZ
Interaction of metastasizing and non-metastasizing tumors with cultured vascular endothelial cells and their underlying lamina
01.01.83 - 31.12.85

Ca 27
M. Bar-Eli, Ben-Gurion Univ.
G. Hämmerling, DKFZ
The molecular genetics of tumor growth
01.07.84 - 30.06.87

Ca 28
R. Kaempfer, Hebrew Univ
P. Krammer, DKFZ
Lymphokine receptors on murine
B- and T-cell tumors
01.07.84 - 30.06.87

Ca 29
A. Raz, A. Ben-Ze'ev, Weizmann Inst.
M. Zöller, DKFZ
Escape mechanisms of metastatic tumor variants
01.07.84 - 30.06.87

Ca 38
Y. Kaufmann, The Chaim Sheba Med. Center
W. Falk (P. Krammer), DKFZ
Induction of cytolyic lymphocytes by cytokines
01.07.87 - 30.06.90

Ca 39
M. Revel, Weizmann Inst.
R. Zawatzky (H. Kirchner), DKFZ
Agents controlling the growth and differentiation of primitive blood lymphomyeloid/erythroid stem cells
01.07.87 - 30.06.90

Ca 41
D. Wallach, Weizmann Inst.
H. Holtmann, Med. Hochschule Hannover
D. Männel (W. Dröge), DKFZ
Mechanisms controlling the response to tumor necrosis factor
01.01.89 - 31.12.91

Ca 42
G. Berke, Weizmann Inst.
W. Dröge, DKFZ
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 perforin(s) in inducing tumor regression
01.01.89 - 31.12.91

Ca 43
E. Kedar, Hebrew Univ.
V. Schirrmacher, DKFZ
Application of human cytokine and effector cells for immunotherapy of human tumors in nude mice
01.01.89 - 31.12.91

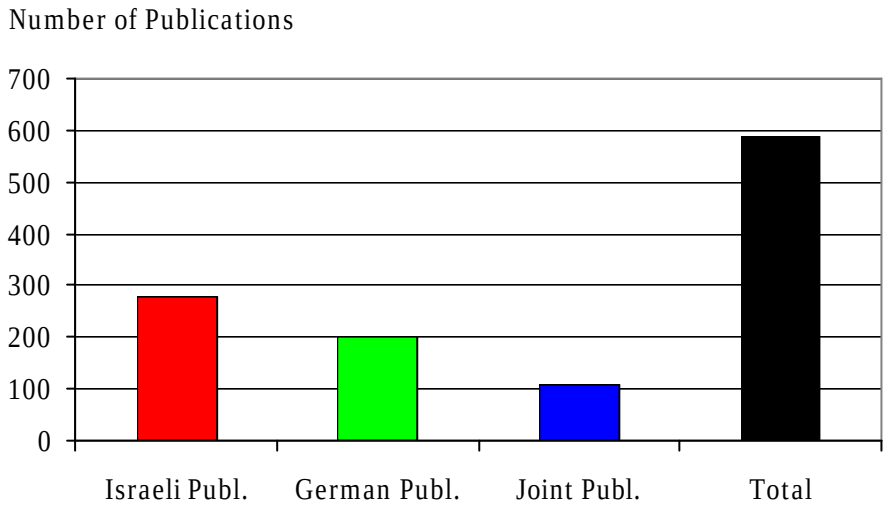
V Ca 44
R.N. Apte, Ben-Gurion Univ.
M. Zöller, DKFZ
Cytokine secretion of tumor cells influence on tumor initiation progression and interaction with the immune system
01.01.89 - 31.12.91

VI Ca 57
G. Neufeld, Technion
R. Schwartz-Albiez (V. Schirrmacher), DKFZ
Growth factor regulated interaction between leukemias/lymphomas and endothelium
01.07.93 - 30.06.96

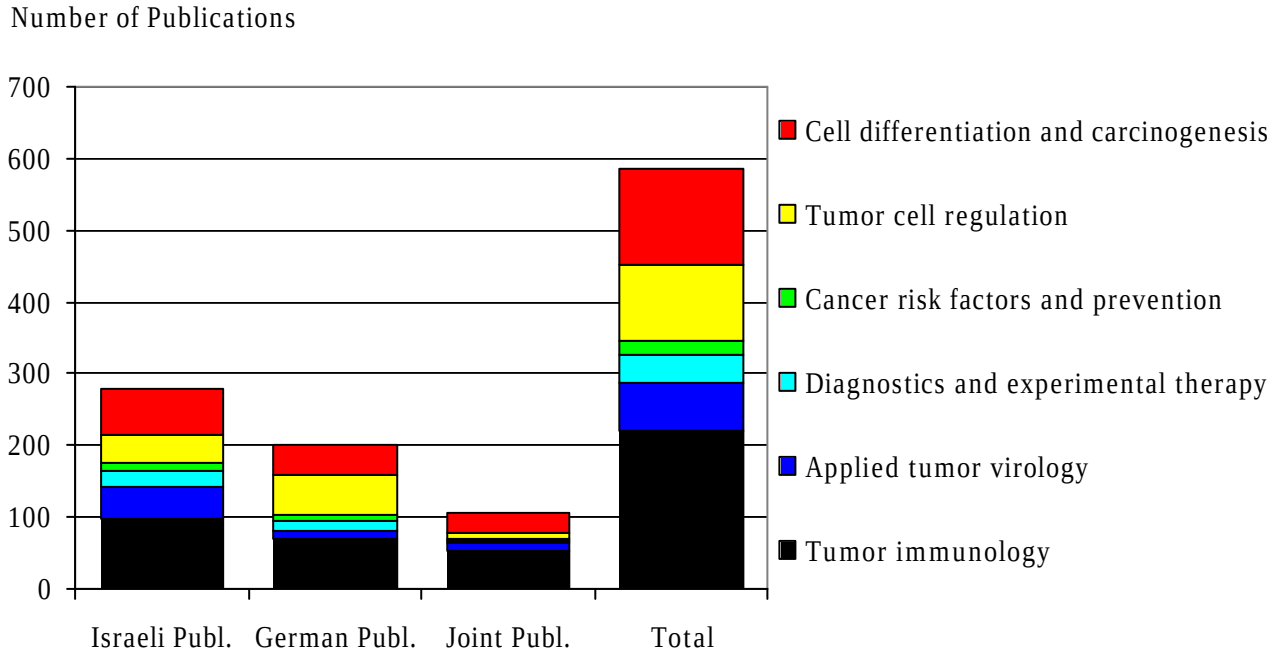
Overview of Publications Resulting from 20 Years of DKFZ-MOS Cooperation in Cancer Research

A. Total Number of Publications
B. Publications According to Research Areas
For Corresponding List of Publications: see Supplement

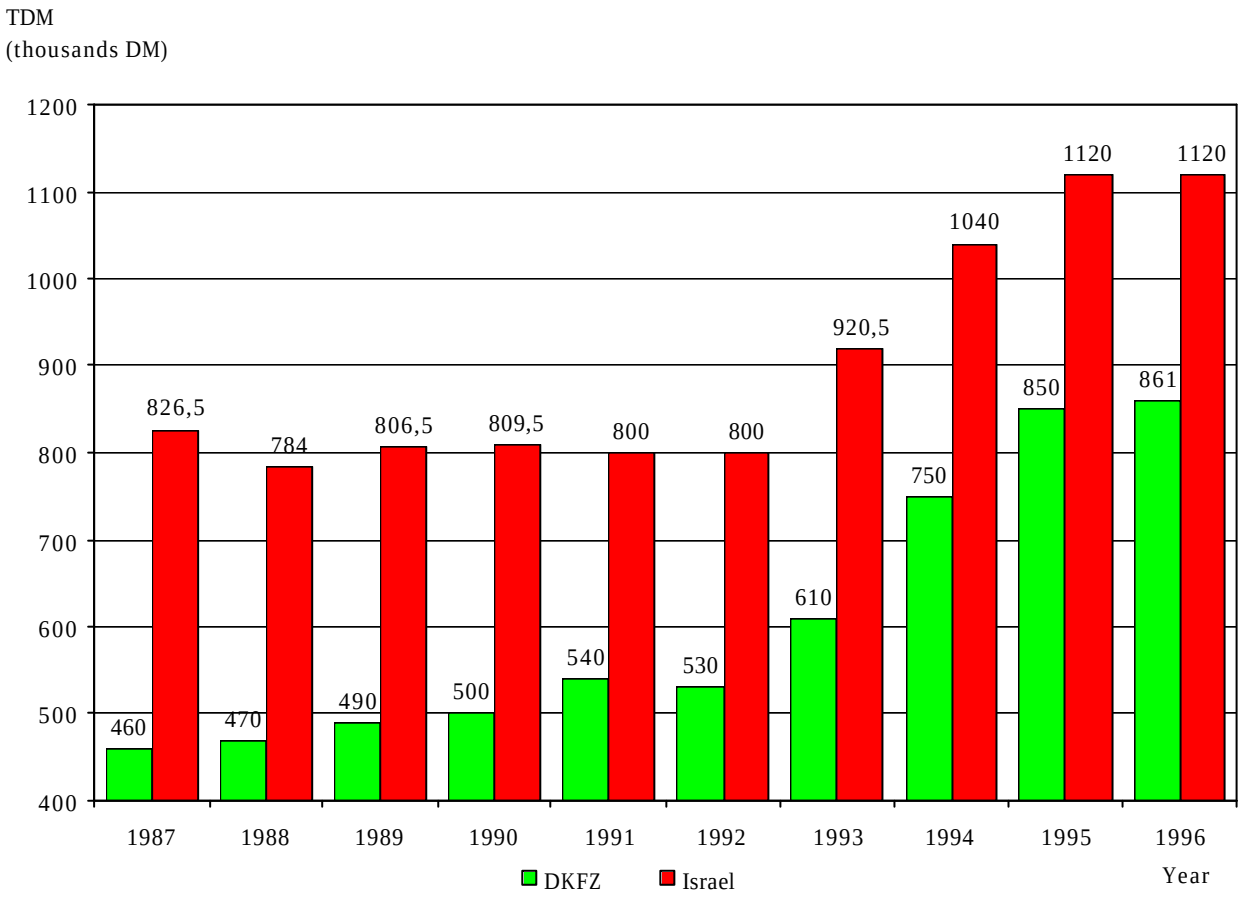
A



B



Overview of Annual DKFZ-Budgets for DKFZ-MOS Cooperation in Cancer Research 01.01.1987 - 31.12.1996



Anniversary Symposium 1997

Symposium
on the Occasion of the 20th Anniversary of the German-Israeli Cooperation Program in Cancer Research

held by
the Deutsches Krebsforschungszentrum
and the Israeli Ministry of Science

on Monday, March 17, 1997

Deutsches Krebsforschungszentrum,
Communication Center, Auditorium

PROGRAM

14.00 - 14.10
Welcome
Prof. Dr. Dr. h.c.mult. Harald zur Hausen
Chairman and Scientific Member of the Management Board
Deutsches Krebsforschungzentrum

14.10-14.25
String Quartet “Petit Versailles”

14.20-14.25
Greetings
Ministerialdirigent Dr. Hans Eschelbacher
Ministry of Education and Research, Bonn

14.25-14.30
Greetings
Naftali Arnon
Deputy Director-General, Ministry of Science, Jerusalem

14.30-15.00
20 Years of Cooperation in Cancer Research with Israel
- a Multidisciplinary Challenge
Prof. Dr. Erich Hecker
Coordinator of the Cooperation Program and Vice-Chairman of the Program Committee
Deutsches Krebsforschungszentrum

15.00 - 15.30
Adhering Cell Junctions of Normal and Transformed Cells
Prof. Dr. Benjamin Geiger
The Weizmann Institute of Science, Rehovot
Prof. Dr. Werner W. Franke
Deutsches Krebsforschungszentrum

15.30 - 16.00
Coffee Break

16.00 - 16.30
Molecular Genetics of an Oncogene (Mdm2) and its Chromosomal Alteration in Pediatric Cancers
Prof. Dr. Moshe Oren
The Weizmann Institute of Science
Prof. Dr. Manfred Schwab
Deutsches Krebsforschungezentrum

16.30 - 16.50
Interferon and Other Ctyokines:
Results and Challenges in Cancer Therapy
Prof. Dr. Michel Revel
Israeli Member of the Program Committee

16.50 - 17.05
Outstanding Activities in the 20 Years of Cooperation
Prof. Dr. Dr. h.c.mult. Harald zur Hausen
awards

- 1. Prof. M. Schlesinger,
Hebrew University, Jerusalem,
Senior Member of the Scientific Program Committee
for his outstanding contributions to the cooperation program
the First ”Wilhelm and Maria-Meyenburg-Lecture” of the DKFZ
- 2. Principal invenstigators of seven cooperation projects recognition as Highlight Projects by the scientific program committee

17.05 - 17.15
String Quartet “Petit Versailles”

17.15 Reception

האיזון העדין יכול להביא למצב של מעט מדי חלבון p53 ולהתהוות סרטן. פרופ' אורן גם גילה שהחלבון p53, הנמצא בתאים של נוירובלסטומה, כנראה נתקע בציטופלזמה ונותר מחוץ לגרעין, שבו הוא היה יכול להיות מועיל ביותר.

פרק מיוחד מוקדש למאמר על אבני-דרך בהתפתחות המחקר הביו-רפואי בתחום הסרטן ולסקירה על תולדות חקר הסרטן בגרמניה ובישראל. מנקודת מבט יותר אישית, פרופ' מיכאל שלזינגר מהאוניברסיטה העברית, פרופ' אריך הקר מה-DKFZ ואחרים משוחחים על ההיסוסים ההתחלתיים ועל ההתפתחות ההדרגתית של קשרי הידידות האישיים שהלכו והתהדקו בין החוקרים משני הצדדים. הם מגיעים להסכמה הכללית הבאה:

ידידות לא ניתן להכתיב, ובמקרה שלפנינו של שיתוף הפעולה בין חוקרי הסרטן הישראליים והגרמניים, היא צמחה מעצמה. אם כי התכנית מוקדשת למטרה מדעית ומקצועית מובהקת, התקדמות בהבנה המדעית כרוכה כמעט תמיד בהתפתחות ההבנה וקשרי הידידות ברמה הבין-אישית.

על-פי בקשת משרדי המדע של גרמניה וישראל נעשתה בפברואר 1997 הערכה של תכנית זו על-ידי צוות מומחים בינלאומיים, בראשות מנהל הסוכנות הבינלאומית לחקר הסרטן (IARC) של ארגון הבריאות העולמי (WHO). בדו"ח הסופי שלהם סיכמו חברי הצוות פה אחד את מסקנותיהם בדברים האלה:

זוהי מסגרת מוצלחת מאד של שיתוף פעולה, אשר צמחה מעשרים השנים האחרונות לא רק במספר הפרויקטים ובהיקף המימון, אלא גם באיכות התשוקה המדעית. התכנית כוללת תחום רחב של נושאים חשובים בחקר הסרטן, החל מהיבטים בסיסיים של טרנספורמציה ממאירה ועד להיבטים קליניים ואפידמיולוגיה. לפיכך חברי הוועדה ממליצים מאד שתכנית זו תימשך ובמידת האפשר תתרחב... הוועדה התרשמה (גם) מן הטיפול המינהלי היעיל של תכנית זו, ואינה מוצאת סיבה לשנות את ההנהלים האדמיניסטרטיביים או הכספיים שהתבשו במהלך שני העשורים שחלפו..

הפרק האחרון של הספר מביא הערכות לגבי עתידה של תכנית מוצלחת זו, מנקודת מבט גרמנית וישראלית.

דרכים למעקב ולבקרה. המסמך הבסיסי "נהלים זמניים ליצירת פרויקטים משותפים" פותח במהלך התכנית במשך תקופה של עשר שנים, ושמו נשמר כדי לציין את מחויבותה של התכנית לבצע באופן תמידי הערכה מחדש, שיפורים ושינויים. מראשיתה עודדה התכנית והמריצה את המשתתפים לקיים ביקורים הדדיים ולבצע במשותף ניסויים מדעיים, מתוך אמונה שהרעיונות הטובים ביותר והידידות הרבה ביותר מתפתחים מתוך מגע אישי הדוק.

ההצלחה המדעית הבלתי רגילה של התכנית זכתה להכרה באופנים שונים. לדוגמה, לפני ארבע שנים החליט הוועד המנהל של ה-DKFZ להשתמש במשאבים העצמיים של המרכז כדי להגדיל את תקציב התכנית המשותפת לרמה של 40% מעל למימון הרגיל שהוקצה מטעם ה-BMBF. רבים מן ההליכים החדשניים של תכנית חקר הסרטן שימשו כדגם לחלקים אחרים של התכנית הכוללת של ה-BMBF ומשרד המדע. הקול-קורא להגשת הצעות מחקר לשנת 1999 משקף את נושאי-העדיפות הנוכחיים של התכנית, כדלהלן:

- היבטים מולקולריים של אפופטוזה בבקרת ממאירויות
- תובנות חדשות בריאורגניזציות גנומיות ייחודיות בתאים סרטניים
- גישות חדשניות לריפוי הסרטן, המבוססות על מטרות מולקולריות ספציפיות

לאחר סקירה מקצועית של הצעות המחקר על-ידי מומחים בעלי שם עולמי באירופה, בארה"ב ובישראל, החברים הישראליים של ועדת התכנית בוחרים מבין ההצעות מספר כפול של תכניות מהמספר שניתן לממן ומעבירים אותן ל-DKFZ לבחינה נוספת. לאחר מכן, ועדת התכנית כולה דנה בהצעות הללו ומקבלת את ההחלטה הסופית.

בשני העשורים האחרונים מומנו למעלה מ-60 פרויקטים של חקר הסרטן, וזאת בשישה תחומים רחבים, אשר במידה רבה גם משקפים את הקדימויות המחקריות של ה-DKFZ:

- התמיינות של תאים והתהוות גידולים ממאירים (13 מחקרים)
- בקרה של תאי גידולים (11 מחקרים)
- גורמי סיכון לסרטן, גילוי מוקדם ומניעה (4 מחקרים)
- דיאגנוסטיקה וריפוי ניסויי (5 מחקרים)
- וירולוגיה יישומית של גידולים (11 מחקרים)
- אימונולוגיה של גידולים (17 מחקרים)

סקירה של אחדים מהפרויקטים מסייעת בהארת מלוא משמעותו של מבצע משותף זה, אשר הוכתר בהצלחה בלתי רגילה. לדוגמה, המענק הגרמני-ישראלי של פרופ' פולקר שירמאכר בשנת 1976 הביא לידי סדרה של מחקרים משותפים שנמשכה למעלה משני עשורים, והפכה אותו לכעין "מדען אורח קבוע" בישראל. חוקר מפורסם זה של ה-DKFZ השתתף בשישה פרויקטי מחקר משותפים. אחד מהם, שבוצע בשיתוף פעולה עם פרופ' ישראל ולודבסקי מן האוניברסיטה העברית, היווה ציון-דרך כמחקר חלוץ בתחום הגרורות. החוקרים הבחירו בהצלחה כיצד תאי סרטן יכולים להמיס ולחדור דרך דפנות של כלי דם ולפלוש לרקמה בריאה. בפרויקט משותף אחר, קבוצות מחקר בראשות פרופ' רולף פליגל מה-DKFZ ופרופ' מרדכי עבוד מאוניברסיטת בן-גוריון חקרו ברמה הגנטית המולקולרית את הגורמים המפעילים את שכפול הרטרו-וירוסים מחוללי הסרטן. את ההתמרה הסרטנית הנגרמת בתאי דם על-ידי נגיף לויקמיה (HTLV-1), מייחסים החוקרים במידה רבה לחלבון Tax-protein שהוא תוצר של הנגיף, ואשר מפעיל מספר גנים חיוניים לו; אבל הם מצאו שהמפעיל הראשוני, שאינו תלוי ב-Tax-protein, נמצא במקום מוקדם יותר בשרשרת השינויים. הם גילו גם מבנה מווסת של רטרו-וירוסים, שלא היה ידוע לפני כן, ואשר מהווה מעורר (פרומוטור) פנימי בנגיף ה-Spuma. שני החוקרים לא רק משלימים זה את זה בכישוריהם המדעיים, אלא הם גם הפכו להיות ידידים טובים המארחים זה את זה בבתיהם ומשלבים תועלת והנאה משיתוף הפעולה ומיחסי הידידות החדוקים.

פרופ' מנפרד שוואב מה-DKFZ, מומחה לנוירובלסטומות (מחלות סרטן של תאי העצבים), ופרופ' משה אורן ממכון ויצמן, מומחה לגן המעכב סרטן p53, חברו יחדיו כדי להראות שהגן הקשור בסרטן mdm2 גורם בתאים אלה לייצור-יתר של חלבוני mdm2, הנקשרים לחלבוני ההגנה p53 ומוציאים אותם מכלל פעולה. מה שגרוע יותר, החלבון p53 מסוגל להתקשר בעצמו ישירות לגן mdm2 ולהגביר את הייצור של חלבון mdm2 על-ידו. המערכת הזו של משוב שלילי היא קריטית, כיוון שפעילות נמוכה מדי של mdm2 עלולה להוביל ליותר מדי חלבון p53 ול"התאבדות" (אפופטוזה) של התאים, ומצד שני ערעור

תקציר

התכנית הגרמנית-ישראלית לשיתוף פעולה בחקר הסרטן נוסדה בשנת 1976 על-ידי המרכז הגרמני לחקר הסרטן (DKFZ) והמועצה הלאומית הישראלית למחקר ופיתוח – כיום משרד המדע. תכנית זו מהווה חלק מתכנית נרחבת יותר לשיתוף פעולה במדע ובטכנולוגיה בין משרד המדע לבין המשרד הפדרלי למחקר ולחינוך (BMBF), תכנית אשר הפעילה עד כה למעלה מ-500 מחקרים גרמניים-ישראליים משותפים, המסתכמים בכ-150 מיליון מרקים גרמניים, מימון שהוענק בעיקר על-ידי ה-BMBF הגרמני. פרויקטים אופייניים מקבלים כ-130,000 מרקים גרמניים בשנה למשך שלוש שנים, והם כוללים מחקר משותף, דו"חות התקדמות, סדנאות ודו"ח סופי משותף. למעלה משישים פרויקטים משותפים המוקדשים לחקר הסרטן, בסכום כולל של יותר מ-20 מיליון מרקים גרמנים, היו מוצלחים במיוחד, הן ברמה המדעית והן ברמה האישית. פעילות מצטיינת זו הניבה למעלה מ-500 מאמרים מדעיים בתחום חקר הסרטן, מהם יותר מ-100 אשר חוברו במשותף על-ידי שני הצדדים. פחות ידועים, אך לא פחות חשובים, הם הקשרים האישיים והמדעיים הממושכים הרבים שנקשרו בין הצדדים המעורבים בנושא.

הדו"ח דלהלן, המתפרסם לציון מלאת עשרים שנה לתכנית חשובה זו, מתחיל בתיאור של הארגונים המכובדים המשתתפים בתכנית משני הצדדים. המרכז הגרמני לחקר הסרטן (DKFZ) נוסד בשנת 1964 כמוסד ציבורי ומאז 1975 הוא מוכר כאחד ממרכזי המחקר הראשיים בגרמניה. ה-DKFZ התקדם במקביל להתפתחויות המהירות בביולוגיה המולקולרית, בטכנולוגיית הגנים ובאימונולוגיה, והוא חלך והתרחב תחת פיקוחם של המועצה המדעית, הוועד המנהל וחבר הנאמנים של המוסד. המרכז כולל עתה 45 חטיבות ויחידות מחקר, המתמקדות בשמונה תחומים עיקריים ובעלי קדימות בתחום חקר הסרטן, החל מבקרה על תאים בגידולים ממאירים ווירולוגיה יישומית של גידולים ועד לביו-אינפורמטיקה. 1600 העובדים של ה-DKFZ כוללים 650 מדענים, העוסקים במגוון רחב של תחומי מחקר. כדי להבטיח הפצה מהירה ויישום קליני של תוצאות המחקרים, ה-DKFZ מקיים גם מספר יחידות של שיתוף פעולה רפואי.

משרד המדע הישראלי, שהוקם בשנת 1982, מקדיש חלק ניכר מפעילותו לקידום מחקר תשתיתי-אסטרטגי, דהיינו מחקר מדעי מכוון בעל היתכנות יישומית ופוטנציאל כלכלי. המשרד פועל להידוק הקשר שבין קהיליות המחקר הבסיסי, הרפואי והתעשייתי של ישראל, וזאת במטרה לקדם את זמן ההבשלה של רעיונות מדעיים משלב המחקר העיוני ועד להעברתם לשלבי המו"פ היישומי. במקביל מקיים משרד המדע קשרי מדע בינלאומיים עם למעלה משלושים ארצות וארגונים, כולל BMBF ו-DKFZ הגרמניים. האגף לקשרי חוץ מדעיים של משרד המדע מנהל הן את התכנית הכוללת לשיתוף פעולה עם ה-BMBF במדע ובטכנולוגיה והן את תכנית שיתוף הפעולה המוצלחת מאד עם ה-DKFZ, וזאת ביחד עם המוסדות הגרמניים המקבילים. המוסדות הישראליים העיקריים אשר נטלו עד כה חלק בתכנית שיתוף הפעולה עם גרמניה בחקר הסרטן כוללים את מכון ויצמן למדע, האוניברסיטה העברית בירושלים, ההסתדרות המדיצינית הדסה, אוניברסיטת תל-אביב, המרכזים הרפואיים סוראסקי ושיבא, הטכניון ואוניברסיטת בן-גוריון.

בסקירה הרטרוספקטיבית הזו של עשרים שנות שיתוף פעולה מוצלח, פרופי אריך הקר, לשעבר יושב ראש מועצת המנהלים של ה-DKFZ, דרי יאיר דגני, ראש האגף למדעי החיים במשרד המדע ואחרים שהיו מעורבים בסיפור יוצא-דופן זה, מזכירים את מקורות התכנית והתפתחותה, המשוכות בהן נתקלה, הצלחותיה ועתידה – הן במישור האישי והן במישור המדעי. בעוד שבתחילה נראתה התכנית כחלק ממאמץ גרמני נרחב להביא ליחסים נורמליים בין גרמניה לישראל לאחר מוראות מלחמת העולם השניה, ומאידך – כחלק ממגמה ישראלית להרחיב ולבסס את מעמדה המדעי הבינלאומי, הרי שעד מהרה הפכה התכנית לשיתוף פעולה פעיל ואמיתי, שבו המשתתפים השילו מעליהם את הסטריאוטיפים הקודמים ויצרו יחסים מתמשכים של שותפות וידידות. כיוון שמחלת הסרטן היא בעיה אנושית אוניברסלית, שאינה מכירה בגבולות מדיניים או גיאוגרפיים, היא מהווה תחום מחקרי המתאים במיוחד לשיתוף פעולה מעין זה.

התכנית יצאה לדרך בשנת 1976 ובהדרגה צברה תנופה. לאחר ביקורו של פרופי הקר בישראל בשנת 1978 הוקמה ועדת תכנית משותפת, אשר פיתחה, פרסמה ומימשה את הנהלים ואת הקווים המנחים של התכנית, ואף גיבשה

דברי ברכה

מזה 25 שנים, החל משנת 1973, מנהלים משרדי המדע של מדינת ישראל ושל הרפובליקה הפדרלית הגרמנית תכנית נרחבת ורב-תחומית של שיתוף פעולה דו-לאומי בתחום המחקר המדעי. הפרסום הנוכחי מציין מלאת עשרים שנה לשיתוף הפעולה בחקר הסרטן, המהווה את אחת התכניות הדיסציפלינריות המצטיינות בתוך המסגרת הגרמנית-ישראלית הכוללת.

במהלך עשרים שנות שיתוף הפעולה בחקר הסרטן, הקציב משרד החינוך והמחקר (BMBF) של הרפובליקה הפדרלית הגרמנית למעלה מ-16 מיליון מרקים גרמניים כמענקים למדענים ישראליים, אשר השתתפו ביותר מ-60 פרויקטים בילטרליים. מימון נוסף לחוקרים גרמניים וישראליים התקבל מן התקציב העצמי של המרכז הגרמני לחקר הסרטן (DKFZ), האחראי להפעלת התכנית המשותפת בחקר הסרטן מטעם ה-BMBF. משרד המדע הישראלי מביע את תודתו העמוקה למוסדות השותפים בגרמניה על תמיכתם הכספית החשובה.

שיתוף הפעולה המדעי בין גרמניה לישראל התפתח בצל המאורעות הרצחניים של השואה ותחת השפעתם. אף על פי כן, עובדה אובייקטיבית היא שעם הזמן, הדגש בקשרים המדעיים שלנו נע יותר ויותר מתמיכה חד-צדדית לשותפות אמיתית בעלת תועלת הדדית לשני הצדדים. כך, בעוד שאסור יהיה לשכוח לעולם את שורשיו ההיסטוריים של שיתוף הפעולה בינינו, אני סמוך ובטוח שכיום ההישגים המדעיים שהושגו לתועלת שני הצדדים מצדיקים בהחלט המשך והגברה של מאמצינו המשותפים, על בסיס של שיקולים מקצועיים בלבד.

הישגי התכנית המשותפת של ה-DKFZ ומשרד המדע בחקר הסרטן מהווים דוגמה מצוינת ליתרונות המדעיים החדדיים ששיתוף הפעולה הגרמני-ישראלי יכול להניב. למעלה מ-500 פרסומים מדעיים המבוססים על פרויקטים שבוצעו במסגרת תכנית זו, כולל כמאה מאמרים שחוברו במשותף על-ידי מדענים ישראליים וגרמניים, מעידים על הרמה המדעית הגבוהה שהושגה על-ידי המדענים שמחקריהם נתמכו על-ידי התכנית. במחקרים אלה הושגו פריצות דרך חשובות, אשר יסייעו בפיתוחם של אמצעים יעילים למניעה ולריפוי של מחלת הסרטן, ועל-ידי כך הן יתרמו לבריאותה ולרווחתה של האנושות כולה.

אני מברך את המדענים הרבים ואת אנשי המינהל, אשר תרמו מכשרונותיהם ולא חסכו מאמצים כדי שהתכנית תזכה להצלחה כה גדולה. משרד המדע מקווה ומאמין ששני העשורים הבאים של שיתוף הפעולה הגרמני-ישראלי בחקר הסרטן יניבו גם הם תוצאות כה פוריות וכה מועילות לשני הצדדים.

סילבן שלום
שר המדע, ישראל

דברי ברכה

שיתוף פעולה מדעי וטכנולוגי במישור הבינלאומי חשוב כיום יותר מתמיד כדי לשמור על השלום או כדי להשיגו, כדי לשפר את חייהם של בני אדם וכדי לקדם התפתחות מתמדת.

שיתוף הפעולה בין הרפובליקה הפדרלית הגרמנית לבין ישראל בתחומי המחקר הבסיסי והיישומי, המתקיים כבר כ-40 שנה, מהווה מרכיב חשוב במיוחד ביחסים הבילטרליים של גרמניה. הממשלה הפדרלית תומכת בשיתוף פעולה זה ומקציבה לו אמצעי מימון. דוגמה לכך היא ההתכנית לשיתוף פעולה בין המרכז הגרמני לחקר הסרטן (DKFZ) לבין משרד המדע הישראלי. למטרת שיתוף פעולה זה העניקה הממשלה הפדרלית ל-DKFZ בהיידלברג כמיליון מרקים גרמניים לשנה מאז 1976, והיא מימנה מספר כולל של יותר מ-80 פרויקטים משותפים. ב-20 השנים הראשונות של שיתוף הפעולה הושלמו בהצלחה 61 פרויקטים משותפים. העבודה הניבה פרסומי שזכו להערכה בקנה מידה עולמי, וזו עדות לאיכותן המדעית של תוצאות המחקרים. התקדמות הראויה לציון מיוחד הושגה בחקירת הבסיס הגנטי-מולקולרי של התהוות הסרטן. הישגים חשובים חושגו גם בהבנת פעולת הגומלין בין תאים סרטניים לבין התאים הסמוכים, וכן בהבנת ההתפשטות שלהם.

אני בטוחה שהפרויקטים המשותפים יוסיפו להניב תוצאות מצוינות, בעלות חשיבות לא רק למחקר הבסיסי, אלא גם במעבר ליישום הרפואי המעשי. אני מאמינה ששיתוף הפעולה המדעי הגרמני-ישראלי, המאופיין על-ידי רמה גבוהה של ידע מקצועי, יוסיף להתפתח בהצלחה בשנים הבאות.

כתוצאה משיתוף הפעולה רב-השנים, התפתח מארג הנשען על קשרים אישיים רבים מעבר למישור המקצועי. היחסים הידידותיים האלה תורמים להגברת ההבנה ההדדית ולהסרת המחיצות בין שתי התרבויות ובין שתי האומות. אני מאמינה שדבר זה אינו נופל בחשיבותו מן ההצלחות המדעיות המשותפות.

אדלגארד בולמן
השרה הפדרלית לחינוך ולמחקר, גרמניה

שיתוף פעולה גרמניה-ישראל
בחקר הסרטן
20 השנים הראשונות

המרכז הגרמני לחקר הסרטן
הייידלברג

משרד המדע
ישראל

1999

שיתוף פעולה בחקר הסרטן

המרכז הגרמני
לחקר הסרטן
היידלברג

מדינת ישראל
משרד המדע
ירושלים

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