

Inaugural Meeting of the Israeli Society for Cancer
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The First meeting of the Israeli Society for Cancer Research was a huge success. As quite common for the Israeli winter, the day which started with an annoying drizzle, turned out, by mid day, to be beautiful and sunny. This meeting brought together a diverse group of close to 600 scientists whose interests span clinical, biochemistry, cell signaling, immunology and tumour biology aspects of cancer research and treatment. The participants came from academia, hospitals, companies and governmental bodies. The topics of the talks and more than 120 posters ranged from basic research on the molecular levels to the most advanced clinical anti-cancer applications, which made this conference very diverse and dynamic. Despite the diversity, a common language emerged during the meeting, which allowed this broad topic of cancer research, and the fight against it, to be addressed from several vantage points. The meeting that took place at the lovely Smolarz auditorium at Tel-Aviv University was honored by the presence of Prof. Anne-Lisa Børresen-Dale, president of The European Association for Cancer Research (EACR) who gave a fascinating talk on molecular profiling of breast cancer and was organized and chaired by Prof. Eliezer Flescher from Tel-Aviv University. The talks were divided into four sessions which started with a session of Molecular Genetics, followed by sessions on Functional Genomics, Cellular Biology of Cancer Progression and ended with an amazing session on Novel approaches to Cancer Therapy.

The first session began with two clinicians who gave epidemiology-based, very informative talks. These talks, by Prof. Gad Rennert (Haifa, Israel) and Prof. Efrat Levi-Lahad (Jerusalem, Israel) focused on two of the most common and deadliest cancer types: colorectal and breast cancer. Gad shared with us results from the Molecular Epidemiology of Colorectal Cancer Study (MECC). This study that covers all incident cases of colorectal cancer diagnosed in northern Israel since 1998, and population-based controls, is aimed at understanding the causes of colorectal cancer and possible means of prevention, employing both, classical risk factors and molecular patterns. One set of results obtained from this study clearly demonstrates that a combination of physical activity, diet rich in vegetables and the use of aspirin and statins carry protective effects against the development of colorectal cancer in people with specific genetic backgrounds. An important conclusion from this study is that by knowing a persons genetic background it is possible for a physician to recommend a specific life style which may help lower the risk for the development of colorectal cancer. In the next talk Efrat tackled the question of the need for BRCA1/BRCA2 mutation screening in the general population. Efrat demonstrated that breast and ovarian cancer risk in BRCA1 and BRCA2 carriers is complex and is affected by both different genetic and non-genetic factors. These results lead to the conclusion that general population screening for BRCA1 and BRCA2 mutations combined with family history, and known environmental risk factors may dramatically reduce the number of breast and ovarian cancer cases.

In a sharp turn, the next two talks focused on new and exiting molecular functions of the important tumour suppressor protein p53. Prof. Moshe Oren (Rehovot, Israel) provided elegant experimental data showing how epithelial

cancer cells overcome the non-cell-autonomous tumour suppressor function of p53 in stromal fibroblasts. For example, p53 is responsible for low levels of the SDF-1 protein in fibroblasts. Thus, mutations in p53 may alter the response of the tumour cells to external signals, in a way that might augment tumour malignancy. Moreover, tumour cells may affect the expression of p53 in neighboring cells. Together these findings emphasize the importance of the "cross-talk" between the tumour and its adjacent, wild type, cells. Prof. Varda Rotter (Rehovot, Israel) described the way her laboratory has established several *in-vitro* transformation models in which normal cells were transformed into cancer cells by well-controlled genetic alterations. These included inactivation of p53, over-expression of mutant p53 and over expression of Ras. Using genome-wide approach, they have started to identify clusters of genes which are involved with specific steps of malignant transformation. One important cluster is the chemokine CXCL1, the Interleukin IL-1 β and the MMP3 protein that degrades ECM components, that are all involved in the "cross-talk" between Ras and p53. Prof. Doron Ginsberg (Ramat Gan, Israel) showed very recent results from a screen that has identified Maspin and PDC4D as genes that are upregulated as a result of a combination between expression of E2F and chemotherapy. They have found that Maspin is important for the E2F and chemotherapy induced apoptosis. Interestingly, both Maspin and PDC4D are targets of the oncogenic miR21. This raises the interesting possibility that the E2F transcription factor regulates the expression of miR21 which in turn silences the expression of Maspin and PDC4D and as a result effect the E2F induced apoptosis.

Next was the fascinating talk by the Key-note speaker Prof. Anne-Lisa Børresen-Dale (Oslo, Norway) who discussed the importance of breast cancer molecular profiling for early diagnosis and treatment. Among women world wide, breast cancer is the most common malignancy and the leading cause of cancer-related death. It is known that breast carcinomas are characterized by frequent chromosomal alterations with biological and clinical significance. As the breast cancer detection methods used today such as mammography and MRI are inadequate for a large number of patients, there is an important need for better and improved detection methods. Anne-Lisa showed us results taken from a large group of patients and controls, that using a simple and cheap blood test it is possible to identify genotypes and gene expression profiles contributing to elevated cancer risk, radiation sensitivity, tumour aggressiveness and therapy resistance. The results of these studies may be used to identify high-risk individuals that may benefit from preventing strategies, and to individualize the treatment of patients with respect to choice of drugs as well as to dose and duration. This may give a better therapeutic effect and less adverse reactions in the individual patient. Anne-Lisa emphasized the important need for large data bases combining all the known risk factors and showed how systematic investigation of genetic variation, both inherited and somatically altered, gene expression patterns and genome wide copy number alterations in human breast and ovarian tumours and their correlation to specific features of phenotypic variations, will provide the basis for an improved molecular taxonomy. When hundreds of tumours have been systematically characterized, a better tumour classification is likely to appear, and statistically significant relationships with different clinical parameters may be uncovered. The results show that a blood-based gene-expression test can be developed to detect breast cancer early in asymptomatic patients.

The second session started with a talk by Prof. Gideon Rechavi (Tel-Aviv, Israel) who discussed the adenosine to inosine (A-to-I) RNA-editing and its importance in cancer. To date there are RNA-editing sites in more than 10,000 genes. These editing events lead to a large diversity of gene expression by changing, among other, amino-acids, splicing sites, RNA stability and interestingly the movement of

RNA into the nucleolus. Another enlightening phenomena is that recent findings demonstrate that RNA-editing is impaired in a very large number of cancer types and may be one of the important causes for the development of these cancer types. Prof. Israel Vlodavsky (Haifa, Israel) demonstrated using a large number of experimental approaches the importance of the endoglycosidase Heparanase in inflammation and cancer progression. Israel demonstrated new findings showing that the C'-terminus of Heparanase, that has no enzymatic activity, is critical for heparanase secretion and signaling function. Currently, Inhibitors directed against the C-terminus domain, combined with inhibitors of heparanase enzymatic activity are being developed to halt tumour growth, metastasis, angiogenesis and inflammation and a lead compound is in clinical trial. Prof. Eli Keshet (Jerusalem, Israel) showed his findings demonstrating that VEGF is responsible for organ homing of circulating cells and is required for their perivascular positioning and retention. Importantly Eli showed that retention of recruited bone marrow-derived circulating cells (RBCCs) by VEGF is mediated by SDF1, a chemokine induced by VEGF. Together, his data suggest a model for VEGF-programmed adult neovascularization highlighting the essential paracrine role of recruited myeloid cells and a role for SDF1 in their perivascular retention. The morning sessions ended by a beautiful and colorful presentation by Dr. Ilan Tsarfati (Tel-Aviv, Israel) who by using double photon confocal microscopy looks at cancer cells at the single cell level. On the cellular level Ilan examines the sub-cellular-localization and expression of the activated Met oncogen. Using the most advanced confocal techniques this laboratory has shown, that Met induces membrane "blebbing" that is important for directional cell movement. These techniques combined with MRI-and-ultrasound-imaging that are used in his laboratory may be used in the future to specifically target breast tumour cells that express activated Met.

The afternoon session opened with a talk by Prof. Dov Zipori (Rehovot, Israel) that through studies on multiple myeloma raises the provocative hypothesis that "cancer stem cells" are actually deprived of stem cells. He provides experimental evidence showing that the cancer cells do not exhibit a phenotype similar to the hemopoietic stem cell and that the molecular nature of the bone marrow niches needed for their proliferation and spread have little resemblance to the structure of the normal hemopoietic stem cell niches. He concludes that a way to fight cancer is to introduce back stem cell phenotypes into cancer cells and not to try and eliminate cancer stem cells. Next, Prof. Michal Neeman (Rehovot, Israel) showed a striking example of results obtained from MRI-based research and demonstrated new possibilities for future gene therapy. Michal showed how non-invasive MRI can be used to demonstrate the rapid angiogenic response induced by tumours, and the inherent instability of immature vessels, lacking the perivascular mural cells. Moreover, she showed that tumour associated fibroblasts and myofibroblasts can be labeled *ex vivo* to allow non-invasive imaging of their recruitment to the tumour vasculature. Prof. Ron Apte (Beer Sheva, Israel) uses knock-out mice models to study the crucial role of microenvironment-derived IL-1 in determining the invasive potential of malignant cells. The last two talks of this session focused on hepatocellular carcinoma. Prof. Eitan Galun (Jerusalem, Israel) is studying the question why does liver regeneration under chronic-inflammation enhance hepatocellular carcinoma? Using partial-hepatectomy in mice Eitan's group were able to show that under regenerative proliferative stress, the genomic-unstable hepatocytes escape apoptosis and reenter the cell cycle, causing the enhanced tumourigenesis induced by liver resection. Dr. Eli Pikarsky ((Jerusalem, Israel), as did the previous speaker, described hepatocellular carcinoma as a disease that almost always develops on the background of chronic liver inflammation. Thus, they set up to understand the mechanisms through which inflammation drives cancer development. They have found that the JNK

pathway is commonly activated in the pre-malignant state and probably functions through phosphorylated c-Jun.

The last session began with a talk by Prof. Yosef Yarden (Rehovot, Israel), and described a strategy of targeting HER2, a protein that is overexpressed in breast cancers. This strategy involves targeting one or all of the known Achilles' heel of HER2, namely the dimerization site, the ATP binding site or/and disrupting the Hsp90-HER2 interactions. Prof. Yoel Kloog (Tel-Aviv, Israel) described the development of Ras inhibitors. The ability to develop such inhibitors results mainly from the amazing basic scientific work this laboratory is doing on the Ras's mechanism of action. One example is using farnesylthiosalicylic acid that acts in a rather specific manner on the active, GTP-bound forms of H-Ras, N-Ras, and K-Ras proteins. Prof. Varda Shoshan-Barmatz (Beer Sheva, Israel) focused on the mitochondrial voltage-dependent anion channel (VDAC) protein which plays a role in mitochondria-mediated apoptosis. Interestingly apoptosis is associated with VDAC oligomerization and VDAC's N-terminal region controls cytochrome c release. Thus, VDAC may be exploited as a new target for cancer therapy. The last topic was presented by Prof. Shimon Slavin (Tel-Aviv, Israel). Using examples of people that have recovered from cancer Shimon suggests that the anti-cancer treatment (high-dose chemoradiotherapy supported by autologous or allogeneic stem cell transplantation) should focus on an attempt to increase the cure rate of high-risk tumours at an early stage of the disease since a stage of minimal residual disease can be accomplished in most patients with cancer.

This enriching and enlightening meeting ended with prizes to the best posters. The prizes were sponsored by EACR and presented by Robert Kenney, EACR Executive Director.

As exemplified by the presentations described above, this exhilarating meeting was a huge success and as Prof. Benjamin Sredni, the Chief Scientist, Ministry of Health, Israel said this is a very important and very much needed conference and we hope that it is the first of many more to come.