THE SIXTH ANNUAL MEETING OF THE ISRAELI SOCIETY FOR CANCER RESEARCH (ISCR)

FROM MECHANISMS TO THERAPIES

The Ruth and Bruce Rappaport Faculty of Medicine
Technion - Israel Institute of Technology
Haifa, 22 May, 2014

SCIENTIFIC PROGRAM

08:00 Gathering and Registration, Poster Viewing and Visit the Exhibition

09:10 OPENING REMARKS
Yuval Shaked, *Chairman of the organizing committee*
Dept. of Molecular Pharmacology, Rappaport Faculty of Medicine, Technion - Israel Institute of Technology, Haifa, Israel
Eliezer Shalev, Dean of Ruth & Bruce Rappaport Faculty of Medicine, Technion - Israel Institute of Technolog, Haifa, Israel
Yona Keisari, President of the Israeli Society for Cancer Research

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09:30 - 11:00 **Session 1** **Ruth Auditorium**

GENETIC AND EPIGENETIC MECHANISMS IN TUMORIGENESIS

Chair: **Sol Efroni**, Israel

09:30 RNF4-MEDIATED AND SUMO-INDEPENDENT ACTIVATION OF ONCOGENIC PATHWAYS BY SELECTIVE PROTEIN STABILIZATION
Amir M. Orian
Rappaport Research Institute and Faculty of Medicine, Technion - Israel Institute of Technology, Haifa, Israel

09:50 NEW INSIGHTS INTO THE EFFECT OF CANCER GENES ON DNA REPLICATION AND GENOME STABILITY
Batsheva Kerem
Dept. of Genetics, Alexander Silberman Institute of Life Sciences, The Hebrew University of Jerusalem, Jerusalem, Israel

10:10 CANCER AND RNA EPIGENETICS
Gidi Rechavi
Dept. of Genetics and Biochemistry and Cancer Research Center, The Chaim Sheba Medical Center, Tel Hashomer, Israel

10:30 ***Keynote Lecture***
REGULATION AND ROLES OF THE P53 PROTEIN IN CANCER
Carol Prives
Dept. of Biological Sciences at Columbia University, New York, NY, USA

11:00 *Coffee Break, Poster Viewing and Visit the Exhibition*

SCIENTIFIC PROGRAM (cont.)

11:20 - 12:45 **Parallel Session 2A** **Ruth Auditorium**

NEW APPROACHES IN CANCER DETECTION, IMAGING AND TREATMENT

Chair: **Alberto Gabizon**, Israel

11:20 REALIZING THE PROMISE OF CANCER IMMUNOTHERAPY
Hyam Levitsky
Global Head Cancer Immunology Experimental Medicine
Hoffmann La Roche, Pharma Research and Early Development, Schlieren, Switzerland
Sponsored by Roche Pharmaceuticals (Israel) Ltd.

11:50 WHOLE-EXOME SEQUENCING IDENTIFIES RECURRENT FUNCTIONAL MUTATIONS IN MELANOMA
Yardena Samuels
Dept. of Molecular Cell Biology, Weizmann Institute of Science, Rehovot, Israel

12:10 MODELING TREATMENT OF ADVANCED METASTATIC DISEASE IN MICE AS A PREDICTIVE CLINICAL BIOMARKER
Robert S. Kerbel
Dept. of Medical Biophysics, Sunnybrook Research Institute, Toronto, Canada

12:30 **DELAYED CONTRAST MRI - A NOVEL TOOL FOR DECISION MAKING IN NEURO-ONCOLOGY
Yael Mardor
Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv; Advanced Technology Center, Sheba Medical Center, Ramat Gan, Israel

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11:20 - 12:40 **Parallel Session 2B** **Red Auditorium**

ADVANCES IN HEMATOLOGICAL MALIGNANCIES

Chair: **Benjamin Brenner**, Israel

11:20 ANTILEUKEMIC POTENTIAL OF COMBINATIONS OF NATURAL AGENTS WITH DISTINCT MECHANISMS OF ACTION
Michael Danilenko
Dept. of Clinical Biochemistry and Pharmacology, Ben-Gurion University of the Negev, Beer Sheva, Israel

11:40 STEM CELL TRANSPLANTATION AND TARGETED THERAPIES IN HEMATOLOGICAL MALIGNANCIES
Arnon Nagler
Hematology Division, BMT and CBB, Chaim Sheba Medical Center, Tel Hashomer, Israel

****Selected Abstract for Presentation**

SCIENTIFIC PROGRAM (cont.)

11:20 - 12:40 **Parallel Session 2B (cont.)** **Red Auditorium**

12:00 INTRA-TUMOR HETEROGENEITY AND RESPONSE TO CHEMOTHERAPY IN ACUTE MYELOID LEUKEMIA (AML) - CHALLENGING THE COMMON IMMUNOPHENOTYPIC DEFINITION OF MALIGNANT CELLS
Yishai Ofran
Dept. of Hematology and Bone Marrow Transplantation, Technion/Rambam, Haifa, Israel

12:20 **MIR-30E TARGETS BCR-ABL1 AND SENSITIZES K562 CELLS TO IMATINIB TREATMENT
Oshrat Hershkovitz Rokah
Felsenstein Medical Research Center, Beilinson Hospital; Sackler School of Medicine, Tel Aviv University, Petah Tikva, Israel

12:40 - 13:00 **ISCR BUSINESS SESSION** **Ruth Auditorium**

13:00 *Light Lunch Break, Poster Viewing and Visit the Exhibition*

14:00 - 15:30 **Session 3** **Ruth Auditorium**

METABOLIC PATHWAYS IN CANCER

Chair: **Amir M. Orian**, Israel

14:00 ***Keynote Lecture***
*MTOR SIGNALING IN GROWTH AND METABOLISM
Michael N. Hall
Biozentrum, University of Basel, Basel, Switzerland

14:30 KLOTHO: FROM AGING SUPPRESSION TO REGULATION OF TUMOR METABOLISM
Ido Wolf
The Oncology Institute, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

14:50 THE ROLE OF SIRT6 IN METABOLISM AND CANCER
Haim Cohen
Molecular Mechanism of Aging Lab, Bar Ilan University, Ramat Gan, Israel

15:10 ELUCIDATING THE ROLE OF LIPOPROTEINS IN TUMOR-RELATED ANGIOGENESIS AND METASTASIS
Karina Yaniv
Dept. of Biological Regulation, Weizmann Institute of Science, Rehovot, Israel

15:30 *Coffee Break, Poster Viewing and Visit the Exhibition*

***In Memory of Prof. Eliezer Flescher**
****Selected Abstract for Presentation**

SCIENTIFIC PROGRAM (cont.)

15:50 - 17:15 **Parallel Session 4A** **Ruth Auditorium**

THE TUMOR MICROENVIRONMENT AND THE IMMUNE SYSTEM

Chair: **Angel Porgador**, Israel

15:50 IMMUNE CHECKPOINT INHIBITORS FOR CANCER IMMUNOTHERAPY
Gal Markel
Ella Institute of Melanoma, Sheba Medical Center, Ramat Gan;
Dept. of Clinical Microbiology & Immunology, Sackler Faculty of Medicine, Tel Aviv University, Israel
Sponsored by BMS Israel

16:20 **THE ROLE OF LONG NON-CODING RNA (MALAT1) IN TUMOR INITIATION AND METASTASIS
Pushkar Malakar
Dept. of Biochemistry and Molecular Biology, Institute for Medical Research Israel Canada (IMRIC), Hebrew University Hadassah Medical School, Jerusalem, Israel

16:35 THE ROLE OF CCR5 IN DIRECTING THE ACCUMULATION OF MYELOID DERIVED SUPPRESSOR CELLS AT THE TUMOR SITE
Nathan Karin
Dept. of Immunology, The Ruth and Bruce Rappaport Faculty of Medicine, Technion Israel Institute of Technology, Haifa, Israel

16:55 THE TUMOR AND STROMA IN BREAST CANCER: INFLAMMATION-DRIVEN PRO-CANCER EFFECTS AND THEIR POTENTIAL THERAPEUTIC IMPLICATIONS
Adit Ben-Baruch
Dept. Cell Research and Immunology, Tel Aviv University, Tel Aviv, Israel

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15:50 - 17:05 **Parallel Session 4B** **Red Auditorium**

CANCER SIGNALING

Chair: **Ami Aronheim**, Israel

15:50 **DIFFERENTIAL METHYLATION OF P73 VARIANT (DELTANP73) IN NORMAL BREAST EPITHELIUM AND SUSCEPTIBILITY TO BREAST CANCER IN BRCA1/2 MUTATION CARRIERS
Ella Evron
Dept. of Oncology, Assaf Harofeh Medical Center, Zerifin, Israel

16:05 SENESCENCE AND THERAPY INDUCED SENESCENCE - ROLE OF PKC
Etta Livneh
The Shraga Segal Dept. of Microbiology, Immunology and Genetics, Ben-Gurion University of the Negev, Beer Sheva, Israel

****Selected Abstract for Presentation**

SCIENTIFIC PROGRAM (cont.)

15:50 - 17:05 **Parallel Session 4B (cont.)** **Red Auditorium**

16:25 FROM TARGETED TO MULTI-TARGETED CANCER TREATMENTS
Alexander Levitzki
Unit of Cellular Signaling, Dept. of Biological Chemistry, The Alexander Silberman Institute of Life Sciences, The Hebrew University of Jerusalem Jerusalem, Israel

16:45 EXPLOITING GLOBAL EFFORTS ON CANCER GENOMIC MUTATIONS TO OPTIMIZE TREATMENT CHOICE FOR OTHERWISE REFRACTORY CANCER CASES
Izhak Haviv
Medicine, Bar Ilan University, Zefat, Israel

17:15 CONCLUDING REMARKS **Ruth Auditorium**
Poster Awards

ABSTRACTS
ORAL
PRESENTATIONS

RNF4-MEDIATED AND SUMO-INDEPENDENT ACTIVATION OF ONCOGENIC PATHWAYS BY SELECTIVE PROTEIN STABILIZATION

Mona Abed[1], Yaniv Zohar[1,2], Rostislav Novak[1,3], **Amir M Orian[1]**
[1]Rappaport Research Institute and Faculty of Medicine, Technion - Israel Institute of Technology, Haifa, Israel, [2]Dept. Of Pathology, Rambam Medical Center, Haifa, Israel, [3]Dept. Of Orthopedics, Rambam Medical Center, Haifa, Israel

Cancer cells rewire genetic networks that together with oncogenes promote tumorigenesis. These genes are key for cancer cells to cope with the "cancer stress response" such as genomic instability, hypoxia and proteotoxic stress. These genes enhance the survival of tumors, and are emerging as potent molecular drug targets. Recently we found that the SUMO-Targeted Ubiquitin Ligase (STUbL) RNF4 is one such target and is of general importance in cancer. Our findings are consistent with reports showing that the SUMO pathway regulates oncogenic networks in cancer. Specifically, we found that RNF4 enhances oncogenes activity within tumorigenic signaling pathways in epithelial cancer cells. In part, RNF4 activity is mediated by stabilizing a subset of short-lived oncogenes. Furthermore, RNF4 is a positive feedback agonist of Wnt/Myc and Notch/Myc pathways in cancer cells, intestinal organoids, and is central for machinery that impact oncogene stability and activity during tumorigenesis. In sum, our study and ongoing work using patient-derived samples revealed a novel fundamental biological concept in protein dynamics highly relevant to cancer, that also holds a promise for the development of future RNF4-based diagnostics and therapeutics highly relevant to colon cancer.

NEW INSIGHTS INTO THE EFFECT OF CANCER GENES ON DNA REPLICATION AND GENOME STABILITY

Assaf Bester, Maayan Roniger, Dan Sarni, Noa Lamm, **Batsheva Kerem**
Dept. of Genetics, Alexander Silberman Institute of Life Sciences, The Hebrew University of Jerusalem, Jerusalem, Israel

Chromosomal instability is a hall mark of cancer. In early stages of cancer development the instability is caused by stress on the DNA replication. However, the molecular basis for this replication perturbation remained unknown. We have studied the replication dynamics in cells enforced to proliferate by aberrant activation of the Rb-E2F pathway, due to over-expression of the viral (HPV-16 E6/E7) or cellular (cyclin E) oncogenes. This enforced cell proliferation with an insufficient pool of nucleotides to support normal DNA replication resulting in replication perturbation, DNA damage and genome instability. Importantly, an exogenous supply of nucleosides rescued the replication stress, decreased the replication-induced DNA damage and reduced transformation. Hence, the low-nucleotide pool is a result of unbalanced activation of nucleotide biosynthesis genes. We have extended the analysis to other cancer genes. Our results shed a new light on the effect of aberrant expression of cancer gene on the replication-induced DNA damage.

Tumorigenicity is driven by alterations in cellular and environmental factors. We further analyzed the effect of folate, an environmental factor essential for nucleotide biosynthesis, on the early stages of cancer. We show that suboptimal levels of folate, which are associated with increased risk of cancer development, lead to concentration-dependent replication-induced DNA damage. Importantly, folate deficiency significantly enhances the replication stress caused by aberrant oncogene expression, leading to significantly increased DNA damage and tumorigenicity. These findings shed new light on the combined effect of cellular and environmental factors on cancer and indicate that the extent of nucleotide-driven replication stress is a key regulator of tumorigenicity.

CANCER AND RNA EPIGENETICS

Gidi Rechavi
Sheba Cancer Research Center, Tel Hashomer, Ramat Gan and Tel Aviv University, Tel Aviv, Israel

RNA comes in many flavors such as mRNA, tRNA, rRNA, siRNA, miRNA, lncRNA, snoRNA and more. To allow the wide spectrum of RNA functions including information encoding, catalytic, regulatory and structural activities, the various RNA molecules are decorated by more than one hundred modifications. While biochemical studies documented the presence of the variety of modified nucleotides in RNA the information regarding the distribution, quantity and function of these modified nucleotides was very limited due to the lack of high throughput methodologies for the identification of such modified nucleotides. Bioinformatics and next generation sequencing based approaches now enable the deciphering of the distribution and role of the modifications. We described the first human adenosine to inosine RNA editome and the first human m6A RNA methylome. Aberrations in these epigenetic RNA regulatory mechanisms were found to be relevant to a variety of human diseases and in cancer in particular. Global RNA editing derangement was demonstrated in several types of cancer. Recently the importance of particular targets of RNA editing was demonstrated in brain tumors, chronic myeloid leukemia and hepatocellular carcinoma. Global m6a methylation dysregulation was associated with cancer predisposition in particular in malignant melanoma.
The study of global RNA epigenetic mechanisms and the characterization of key enzymes involved in such epigenetic regulation may be utilized for the development of new therapeutic approaches.

REGULATION AND ROLES OF THE P53 PROTEIN IN CANCER

Carol Prives
Dept. of Biological Sciences, Columbia University, New York, NY, USA

The p53 protein is a sequence-specific transcriptional regulator of multiple genes that control processes associated with tumor suppression such as cell cycle arrest, cell death, senescence, and metabolic homeostasis. It is held in check by two closely related proteins, Mdm2 and MdmX that work in concert to repress p53 as a transcriptional activator and also to degrade p53 in unstressed cells. While wild-type p53 is an extensively studied and validated tumor suppressor, epidemiological studies, mouse models and cell based assays support the likelihood that the mutant forms of p53 found in many tumors contribute to pro-oncogenic activities such as motility, invasion and metastasis. I will discuss recent studies that have revealed novel pathways in which p53 operates and new regulators of p53 and Mdm2. In each case datasets from cancer patients have supported the potential clinical relevance of our basic research findings.

REALIZING THE PROMISE OF CANCER IMMUNOTHERAPY

Hyam Levitsky
Global Head Cancer Immunology Experimental Medicine
Hoffmann La Roche, Pharma Research and Early Development,
Schlieren, Switzerland

The generations-old dream of harnessing the host immune system to treat cancer has now shown unequivocal signs being fulfilled. The demonstration that immune recognition and evasion are key events in neoplastic transformation and progression, together with the identification of molecular targets responsible for immune regulation has led to immune-based therapies that sometimes result in dramatic and durable clinical responses across a range of solid and hematologic malignancies. These early successes have provided unprecedented insight into the features predictive of, and responsible for disease control with such approaches. Importantly, as single agents, the frequency of response is highest in subjects who have clear evidence of a pre-treatment endogenous immune response ongoing in the tumor microenvironment. Yet the reasons responsible for the absence such responses in the majority of patients with common solid tumors are not clear, nor are the implications for how to optimally develop immunologic approaches in such settings. One consequence of the targets of immune therapy being components of the immune system itself rather than cancer cell intrinsic pathways is that the kinetics and pattern of clinical responses (including disease stabilization) differ significantly when compared to conventional cytotoxic or molecular targeted chemotherapies. Such differences have led to the realization that the metrics used in clinical development of classical cancer drugs are often not well suited for novel immunotherapies. Of particular importance is the recognition that a given immunotherapeutic "drug" may achieve biological endpoints that are necessary but not sufficient for clinical benefit. Based on these observations, extensive pre-clinical data, and early clinical trial results, it has become plainly evident that the next major opportunity for increasing the rate and depth of clinical responses is with combination immunotherapies. In principle, agents acting on distinct, complementary events in the host antitumor immune response are most likely to demonstrate therapeutic synergy. These events range from T cell priming, to clonal expansion, effector cell differentiation and immunologic memory, leukocyte trafficking, and execution of effector function, overcoming features of the tumor microenvironment that have often been selected for silencing immune activation. This biological reality has led to the need for strategic thinking about the best way such combinations can most effectively be tested and developed. The challenges will be discussed, together with some potential solutions.

WHOLE-EXOME SEQUENCING IDENTIFIES RECURRENT FUNCTIONAL MUTATIONS IN MELANOMA

Jared J. Gartner[1], Stephen C. J. Parker[1], Todd D. Prickett[1], William Robinson[2], Steven Robinson[2], Steven, A. Rosenberg[3], Francis S. Collins[1], Nicholas K. Hayward[4], **Yardena Samuels[5]**

[1]National Human Genome Research Institute, NIH, Bethesda, MD, USA [2]University of Colorado School of Medicine, Aurora, CO, USA, [3]National Cancer Institute, NIH, MD, USA, [4]Queensland Institute of Medical Research, Brisbane, QLD, Australia, [5]Molecular Cell Biology Dept., Weizmann Institute of Science, Rehovot, Israel

Cancer is a genetic disease that involves the accumulation of somatic mutations. Advances in high-throughput genomic technologies provide an unprecedented opportunity to interrogate the cancer genetic landscape. However, although ample genomic sequences are available, these have provided limited information concerning the complexity of the cancer genome. Furthermore, our understanding of the functional effects of identified mutations is hampered by the difficulty in assessing their biological effects in a physiological manner. This gap between our knowledge of genetic alterations and our understanding of their functional effects is a re-occurring theme in the cancer genetics field. As more cancer genes become identified through sequencing approaches, attention will shift away from identification of cancer genes towards determining the functions they control. To this end, we are establishing high-throughput applications of somatic cell knockout technologies to evaluate newly discovered mutations, such as the mutations we identified in the ionotropic glutamate receptor, GRIN2A and MAP3K5 (mitogen-activated protein kinase kinase kinase-5).

Importantly, synonymous mutations, which do not alter the protein sequence, have been shown to affect protein function. However, synonymous mutations are rarely investigated in the cancer genomics field. Our analysis of our melanoma exomes identified one synonymous somatic mutation in *BCL2L12* (F17F) to occur in 12 out of 285 samples. This led to increased *BCL2L12* mRNA and protein levels, due to differential targeting of wild-type and mutant *BCL2L12* by hsa-miR-671-5p. Protein made from mutant *BCL2L12* transcript bound p53, inhibited UV-induced apoptosis more efficiently than wild-type BCL2L12 and reduced endogenous p53 target gene transcription. This is the first report of positive selection of a recurrent somatic synonymous mutation in cancer. Our data indicate that "silent" alterations have a role to play in human cancer, emphasizing the importance of their investigation in future cancer genome studies.

MODELING TREATMENT OF ADVANCED METASTATIC DISEASE IN MICE AS A PREDICTIVE CLINICAL BIOMARKER

Robert S. Kerbel
Dept. of Medical Biophysics, Sunnybrook Research Institute, Toronto, Canada

A continuing problem in experimental therapeutics cancer research is the tendency of preclinical mouse tumor therapy models to vastly overpredict subsequent clinical trial outcomes of the same or similar therapy. Highly positive preclinical results are usually followed by complete failure in the clinic. The great majority of such preclinical models, whether they involve transplanted or spontaneously arising cancer involve treatment of primary tumors – not advanced metastatic disease, which is typical of patients enrolled in most clinical trials – and a much more challenging circumstance to successfully treat. Therefore, as an approach to help resolve this discrepancy between preclinical and clinical outcomes, we have developed multiple models of postsurgical advanced systemic metastatic disease in mice using human tumor xenografts. They mostly involve using established cell lines of breast, renal, colorectal, liver, and ovarian cancer, as well as melanoma, and this approach is now being extended to patient-derived xenografts (PDXs). The potential promise of this strategy will be discussed by summarizing therapy results using such preclinical metastatic models (in complete contrast to primary tumor therapy studies) which correlated with prior positive or negative outcomes of phase III trials using antiangiogenic drugs, and by 'prospective' studies designed to develop a new effective treatment strategy concept which then went forward for evaluation in phase III clinical trial development with positive results. The latter involves the use of low dose 'metronomic' chemotherapy in combination with an antiangiogenic drug (bevacizumab) used either upfront or as a follow-up maintenance treatment strategy in patients with metastatic disease after initial induction therapy using standard chemotherapy. As a result of these encouraging findings studies are now also underway to develop models for the 'adjuvant' metastatic treatment of early stage microscopic disease and also for neoadjuvant therapy of primary tumors.

DELAYED CONTRAST MRI - A NOVEL TOOL FOR DECISION MAKING IN NEURO-ONCOLOGY

Leor Zach[1,2], David Guez[3], David Last[3], Dianne Daniels[3,2], Yuval Grober[4], Ouzi Nissim[4], Chen Hoffmann[5,2], Dvora Nass[6], Alisa Talianski[7], Roberto Spiegelmann[4,2], Galia Tsarfaty[5,2], Sharona Salomon[3], Moshe Hadani[4], Andrew Kanner[8], Deborah Blumenthal[9], Felix Bukstein[9], Michal Yalon[10], Jacob Zauberman[4], Jonathan Roth[8], Yigal Shoshan[11], Evgeniya Fridman[12], Marc Wygoda[13], Dror Limon[14], Tzahala Tzuk[15], Zvi Cohen[4,2], **Yael Mardor[16,2]**

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Introduction: Conventional MRI is unable to differentiate tumor from non-tumoral enhancing tissues on conventional T1-MRI (such as radionecrosis). We have applied delayed contrast MRI for calculating high resolution maps clearly differentiating tumor/non-tumoral tissues.
Methods: 485 maps were calculated for 144 patients with primary/metastatic brain tumors post treatment recruited to the study and followed using the maps. The maps were validated by comparing pre-surgical maps of patients undergoing surgery during the study with histology.
Results: 52 stereotactic tissue samples and 32 resected lesions acquired from 48 patients with primary/metastatic brain tumors were histologically examined showing near complete agreement with the pre-surgical maps. This validation confirms that blue regions in the maps (efficient clearance of the contrast agent >1hr post contrast injection) represent morphologically active tumor while red regions (contrast accumulation) represent non-tumor tissues. In addition, the maps were used for making 219 decisions. In 61 cases the decision was to continue follow-up (no treatment change); In 158 cases the decision was to change treatment (including surgery, chemoRT, RT, Avastin, SRS etc).
Conclusions: Delayed MRI enables complete separation between tumor (negative signal) and treatment effects (positive signal) with no overlap. In addition it enables using robust MR sequences resulting in high resolution maps clearly depicting tumor/non-tumor tissues. The maps are being used for routine neuro-oncological clinical decisions in Israel (5 major hospitals). Histological validation together with extending to 3D maps of 1mm3 resolution, suggests that the maps may be also applied for planning high precision procedures such as biopsies, resections, SRS, FSR and more.

ANTILEUKEMIC POTENTIAL OF COMBINATIONS OF NATURAL AGENTS WITH DISTINCT MECHANISMS OF ACTION

Victoria Novik[1], Stella Pesakhov[1], Zeev Barvish[1], Daniel Fishman[2], Yoav Sharoni[1], George P Studzinski[3], **Michael Danilenko**

[1]Dept. of Clinical Biochemistry and Pharmacology, Ben-Gurion University of the Negev, Beer Sheva, Israel , [2]Dept. of Physiology and Cell Biology, Ben-Gurion University of the Negev, Beer Sheva, Israel , [3]Dept. of Pathology and Laboratory Medicine, Rutgers New Jersey Medical School, Newark, NJ, USA

Acute myeloid leukemia (AML) is characterized by the uncontrolled growth of poorly differentiated myeloid blasts and is one of the deadliest types of cancer in adults. Standard chemotherapy is ineffective for most patients with AML while the development of targeted therapeutics is hampered by a highly heterogeneous nature of this disease. The global aim of our preclinical research is to establish therapeutic and preventive potential of multitargeted combinations of phytochemicals (e.g., plant polyphenols) and differentiation inducers (vitamin A and D derivatives) which can synergistically affect AML cells at bioavailable concentrations. We have shown that certain polyphenols can markedly enhance the differentiation of AML cells induced by 1,25-dihydroxyvitanin D3 (1,25D) and all-trans retinoic acid. Furthermore, combined treatment with low-calcemic 1,25D analogs and polyphenol-enriched plant extracts produced strong cooperative antileukemic effects in syngeneic mouse models of AML. Our mechanistic data suggest that the synergistic differentiation-inducing effects of 1,25D and polyphenols are medicated by the cooperative activation of the Nrf2 and AP-1 transcription factors leading to functional upregulation of the vitamin D receptor complex. Further, we have identified specific combinations of polyphenols which can synergistically suppress cell growth and induce robust apoptosis in various AML cell lines in the absence of differentiation inducers. Remarkably, such combinations were found non-cytotoxic to different types of normal cells. The obtained evidence indicates that the central mechanism underlying the synergistic antileukemic activity of some polyphenol combinations is the disruption of intracellular calcium homeostasis in AML cells. These results may provide the basis for novel selective combinatorial approaches to treat primary AML and to prevent both the recurrences and secondary AML which can develop from myelodysplastic syndromes or after exposure to alkylating agents. (Supported by the Israel Science Foundation grant 635/11 to M.D. and Y.S. and by the American Institute for Cancer Research grant #10A049 to G.P.S. and M.D.).

STEM CELL TRANSPLANTATION AND TARGETED THERAPIES IN HEMATOLOGICAL MALIGNANCIES

Arnon Nagler
Hematology Division, BMT and CBB, Chaim Sheba Medical Center,
Tel Hashomer, Israel

Allogeneic hematopoietic stem cell transplantation (allo-SCT) is a very effective therapeutic modality with curative potential in patients with hematological malignancies. The therapeutic efficacy is mainly based on the alloreactive reaction of donor lymphocytes against malignant cells of the recipient named as ''graft versus leukemia'' or ''graft versus tumor'' (GVL, GVT) effect. However besides the beneficial GVL effect, alloreactive reaction attacks normal cells and provoke the deleterious ''graft versus host disease'' (GVHD) which represents the major limitation of allo-SCT. Current trials have focused on a dual goal: augmentation of GVL and complete abolishment of GVHD. From a theoretical point of view complete dissociation of GVL from GVHD can occur by selecting antigenic targets present on malignant and absent from normal cells. Hematopoietic tissue restricted minor histocompatibility antigens and leukemia or tumor associated antigens are ideal candidates for tumor targeted immunotherapy. Other options for inducing anti-tumor immunity in the absence of GVHD is Natural Killer (NK) cell immunotherapy, and amplification of immune responses by using monoclonal antibodies, and bispecific T and NK-cell engagers. Genetically modified immune effectors such as T-cells armed with chimeric antigen receptors (CAR) or transduced with T-cell receptors with antitumor specificity is another exciting field of immunotherapy against malignancies.

INTRA - TUMOR HETEROGENEITY AND RESPONSE TO CHEMOTHERAPY IN ACUTE MYELOID LEUKEMIA (AML) - CHALLENGING THE COMMON IMMUNOPHENOTYPIC DEFINITION OF MALIGNANT CELLS

Yishai Ofran[1], Elina Starosvetsky[2], Ido Shlomovich[2], Elinor Sabag[3], Shai Shen Orr[2], Michal Hayun[4]

[1]Dept. of Hematology and Bone Marrow Transplantation, Technion/Rambam, Haifa, [2]Faculty of Medicine, Technion - Israel Institute of Technology, Haifa, [3]Dept. of Hematology, Technion/rambam, Haifa, [4]Dept. of Hematology, Technion/rambam, Haifa, Israel

Clonal heterogeneity has been increasingly appreciated as a common genetic feature of cancer, and poses major challenges to its treatment. However, the correlation between genetic and phenotypic heterogeneity has not been clearly illustrated. In acute myeloid leukemia (AML), sub-clonal shifting from diagnosis to relapse was reported and may reflect heterogeneity within the quiescent leukemia stem cell population or leukemia early precursors which usually survive chemotherapy. In clinical practice, immunophenotyping is widely in use for monitoring disease burden and response to therapy. Usually, only cells within a predefined "blast gate" are considered malignant by their phenotype. We herein demonstrate that in some AML patients, a minor leukemic sub-population reside outside of the common "blast gate" can be identified as the major resistant sub-population and the source for future relapse. The presence of leukemia specific mutations in such sub-population challenges the common immunophenotypic definition of malignant cells.

Sequential bone marrow aspirations from AML patients assigned for the standard intensive chemotherapy induction protocol (7+3) were obtained on diagnosis, the fifth and 14th days of therapy and upon recovery. Leukemic sub-populations were characterized using detailed immunophenotyping by FACS and CyTOFF analysis. The average number of identified sub-populations decreases from 5 at diagnosis to three by the fifth day of therapy. Utilizing a comprehensive panel of 35 antibodies by CyTOFF confirmed the presence of multiple sub-populations with different eradication rate during induction therapy. In four patients, a minor sub-populations that resides outside of traditional "blasts gate" but expresses pathological expression, were the slowest to disappear. In two patients who experienced relapse, the phenotype at relapse resembled the immunophenotype of that minor sub-population. The presence of flt3-itd mutation in minor sub-population sorted by cd34 expression confirmed its leukemic origin.

In AML, malignant cells may express various immunophenotypes not necessarily confined to the common pre-defined blasts gate. Sub-populations which survive to the fifth day of therapy are more likely to be resistant to chemotherapy and may be the seeds for future relapse.

MIR-30E TARGETS BCR-ABL1 AND SENSITIZES K562 CELLS TO IMATINIB TREATMENT

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Chronic myeloid leukemia (CML) is a myeloproliferative disorder carrying the Philadelphia chromosome and an oncogenic BCR-ABL1 fusion gene. Imatinib, a BCR-ABL1 tyrosine kinase inhibitor (TKI) is used as the first line therapy for newly diagnosed CML patients. MicroRNAs (miRNAs) are conserved small non-coding RNAs that negatively regulate gene expression. miRNAs are known to have a causal role in cancer initiation and progression. We compared the miRNA expression pattern of 2 BCR-ABL+ CML cell lines (K562, Meg-01) in reference to healthy blood. In addition, we looked into the expression profile of K562 cells treated with 2 types of TKIs; imatinib and dasatinib. The expression level of 73 miRNAs in K562 and Meg-01 cells was opposite to their expression in normal blood. Of these miRNAs, the expression of 14 miRNAs (miR-23b, 30e, 154, 454, 564, 671-5p, 765, 9, 193b, 320a, 320b, 500, 132, 892) was restored following exposure to TKIs. The reduced expression of miR-30e was one of the most significant changes detected in our setting. In compliance with the cell lines, miR-30e expression was downregulated in primary CML samples and was restored after imatinib treatment. We next assessed the possibility that this miRNA targets BCR-ABL. Indeed, bioinformatics revealed a conserved target site for miR-30e in the 3'-UTR of the ABL1 gene. Overexpression of miR-30e led to a downregulation of BCR-ABL1 and ABL1 protein expression and to reduced expression of the BCR-ABL1 target p-CrkL, signifying a decline in BCR-ABL1 activity. Based on luciferase assays, ABL1 was indeed shown to be a miR-30e target. Lastly, miR-30e promoted a 2-fold induction in imatinib-mediated apoptosis. Although further analyses and patient studies are required, these data suggest that miR-30e may function as a tumor suppressor miRNA implicated in the pathogenesis of CML and its clinical response to imatinib. Furthermore, the combination of TKI treatment and miR-30e present therapeutic potential for CML.

MTOR SIGNALING IN GROWTH AND METABOLISM

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TOR (target of rapamycin) is a highly conserved serine/threonine kinase that controls cell growth and metabolism in response to nutrients, growth factors, cellular energy, and stress. TOR was originally discovered in yeast but is conserved in all eukaryotes including plants, worms, flies, and mammals. The discovery of TOR led to a fundamental change in how one thinks of cell growth. It is not a spontaneous process that just happens when building blocks (nutrients) are available, but rather a highly regulated, plastic process controlled by TOR-dependent signaling pathways. TOR is found in two structurally and functionally distinct multiprotein complexes, TORC1 and TORC2. The two TOR complexes, like TOR itself, are highly conserved. Thus, the two TOR complexes constitute an ancestral signaling network conserved throughout eukaryotic evolution to control the fundamental process of cell growth. As a central controller of cell growth, TOR plays a key role in development and aging, and is implicated in disorders such as cancer, cardiovascular disease, obesity, and diabetes. While the role of TOR in controlling growth of single cells is relatively well understood, the challenge now is to understand the role of TOR signaling in disease and in coordinating and integrating overall body growth and metabolism in multicellular organisms. This will require elucidating the role of TOR signaling in individual tissues. Data on the role of mTORC1 and mTORC2 in controlling cellular processes and in specific tissues will be presented.

KLOTHO: FROM AGING SUPPRESSION TO REGULATION OF TUMOR METABOLISM

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Klotho is a transmembaranal protein which can be cleaved, shed and act as a circulating hormone. Klotho-deficient mice (*kl/kl*) show a shortened life span and multiple disorders resembling human aging, while overexpression of klotho increases lifespan. High klotho expression was noted in the distal convoluted tubules in the kidney and the choroid plexus, but klotho is also expressed in endocrine-related tissues and the gastro-intestinal tract.
In recent years, we and others identified klotho as a potent tumor suppressor in wide array of malignancies, including breast, pancreatic, colon and ovarian cancers. Klotho is epigenetically silenced in early stages of tumorigenesis and re-expression of klotho, or treatment with soluble forms of it, modulates major signaling pathways and inhibits growth of cancer cells in vitro and in vivo.
In mice, the anti-aging properties of klotho have been attributed to its ability to inhibit the insulin and insulin growth factor-1 (IGF-1) pathways, regulate glucose metabolism and protect cells from oxidative stress. Our studies indicated klotho as a potent inhibitor of the insulin and IGF-1 pathways in cancer. We, therefore, hypothesized that klotho may serve as a regulator of metabolism and response to oxidative stress in cancer cells as well.
In order to study the effect of klotho on tumor metabolism, we conducted an NMR-based screen as well as by direct measurements of ATP, lactate and glucose levels. Treatment with klotho attenuated ATP and lactate levels and was associated with activation of AMP-activated protein kinase (AMPK) a major regulator of cellular energy homeostasis. Surprisingly, while klotho protected normal cells from oxidative stress, it increased the sensitivity of cancer cells to such stimuli. Structure function analyses pointed the KL1 domain of klotho as key regulator responsible for these activities.
These studies shed new light on the tumor suppressor activities of klotho and indicate it as a potential regulator of tumor metabolism. As altered cellular metabolism is a process common in a wide range of cancer cells, regulation of cellular metabolism can explain the ability of klotho to affect diverse malignancies.

THE TUMORIGENESIS ASPECT OF MOUSE MODELS OF LONGEVITY

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A striking link exists between advanced age and increased incidence of cancer. However, it is still elusive why aging is a main risk for cancer. The sirtuins are highly conserved enzyme homologues of the yeast Sir2, with activities of NAD+ dependent deacetylase and/or mono ADP ribosyltransferase. A long line of evidence has implicated sirtuins in regulating the aging process of yeast, worms, flies, and rodents. Moreover, much work has been published on the important role of sirtuins in several age-related diseases such as diabetes type II, and cancer. Within the seven mammalian sirtuins, SIRT1 to SIRT7, SIRT6 was shown to positively regulate lifespan and healthspan in particular age related metabolic diseases. Moreover, recent study found that SIRT6 is a tumour suppressor that modulates aerobic glycolysis and inhibits ribosome biogenesis. Here, we will discuss the different functions of SIRT6 as a model to understand the connection between aging and cancer.

ELUCIDATING THE ROLE OF LIPOPROTEINS IN TUMOR-RELATED ANGIOGENESIS AND METASTASIS

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Tumor angiogenesis has been established as a key player in tumor growth and metastases, and has been highlighted as a therapeutic target. Nevertheless, the molecular and physiological regulation of tumor vessels by metabolic determinants in general, and lipids in particular, is largely uncharted. A previous report from our laboratory uncovered a deleterious role of ApoB-Lipoproteins (LIPs) as direct inhibitors of developmental angiogenesis. In this work, we extend our observations from the developing embryo to pathological conditions, and demonstrate that the anti-angiogenic effects of ApoB-LIPs are recapitulated during tumor-promoted angiogenesis. A tight regulation of tumor-related vessel growth, along with strong effects on tumor metastasis, are observed in hyperlipidemic mice. By isolating tumor-related endothelial cells and analyzing gene expression, we characterize the molecular mechanisms underlying the response of tumor endothelial cells (ECs) to lipoproteins. We find that ApoB and ApoE, the protein components of lipoproteins, differentially regulate gene expression within ECs. Taken together our results increase our understanding on the unexplored role of LDL-cholesterol in the regulation of tumor angiogenesis and malignancy. Furthermore, current tumor treatments could potentially benefit from the elucidation of lipid metabolism effects on tumor malignancy and angiogenesis.

IMMUNE CHECKPOINT INHIBITORS FOR CANCER IMMUNOTHERAPY

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Cancer immunotherapy is revolutionizing these days the field of medical oncology. While the idea of harnessing the immune system against cancer is over a century old, insights obtained only recently has enabled the development of innovative drugs carrying significant overall survival benefit in a potentially broad spectrum of malignancies. Immune checkpoints are endogenous regulatory mechanisms that maintain immunological balance and homeostasis along the course of the normal immune response. Targeting these mechanisms, which are sometimes even hijacked by cancer cells to evade the immune system, comprises the mainstay of current immunomodulatory therapeutic approach. Here, the scientific basis and leading drugs and compounds in development will be reviewed.

THE ROLE OF LONG NON-CODING RNA (MALAT1) IN TUMOR INITIATION AND METASTASIS

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Transcriptome analysis of human genome has identified numerous RNAs that do not code for proteins. These non-coding RNAs are either small (sncRNA) or long (lncRNA). Substantial amount of information is available about SncRNA but very little is known about lncRNA. One of the lncRNA is MALAT1 (Metastasis associated lung adenocarcinoma transcript 1). It was discovered as highly expressed transcript in lung cancer. MALAT1 had been shown to be upregulated in various cancers. The biological and functional relevance of this upregulation is not known and is still an enigma. Does MALAT 1 plays a direct role in cancer and metastasis is an open question. Here we explored the role of MALAT 1 in tumor initiation in hepatocellular mouse model and metastasis in breast cancer model. Overexpression of MALAT1 results in upregulation of the splicing factor oncoprotein SRSF1. This upregulation is mediated by the increase in the transcription level of SRSF1 gene as well as decrease in SRSF1 mRNA degradation by nonsense mediated decay. Furthermore, in MALAT1 overexpressing cells, alternative splicing of SRSF1 splicing targets is altered, suggesting that SRSF1 upregulation by MALAT1 changes the cellular alternative splicing program in these cells. Cells overexpressing MALAT1 showed increased proliferative capacity, resistance to anisomycin induced cell death, increased anchorage independent cell growth and formed tumors in mice. Overexpression of MALAT1 in breast cancer cells, increased their metastasis into the lungs. Knockdown of MALAT1 results in down regulation of SRSF1 expression, and inhibition of proliferation and anchorage independent growth. Our findings suggest that MALAT1 acts as a bona fide proto-oncogene in hepatocellular carcinoma development and as an inducer of breast metastasis and can serve as a new target for cancer therapy.

Keywords: MALAT 1, SRSF1, Alternative Splicing, Oncogene, Metastasis

THE ROLE OF CCR5 IN DIRECTING THE ACCUMULATION OF MYELOID DERIVED SUPPRESSOR CELLS AT THE TUMOR SITE

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We have previously shown that the interplay between CCL2 and its CCR2 receptor on tumor associated macrophages (TAMs) is essential for the mobilization of these cells from the bone marrow to the blood and for their colonization at the tumor site to support tumor development and angiogenesis (Izhak et al J. Immunol 2009, Izhak et al, J. Immunol 2010, Izhak et al , Plose One 2012). The driver of myeloid derived suppressor cells (MSDC, CD11b+ Gr1+) mobilization from the BM to the blood and from there to the tumor site is still elusive. It has been shown that individuals with a functional mutation in the CCR5 receptor (delta 32) display a high state of resistance to cancer diseases, hence the underlying mechanism is un-known. Here we use two different immunocompetent models of cancer diseases: a TRAMP mice model of prostate cancer, and the ret model of melanoma, in which CCR5-/- mice are bearing CCR5+ tumors to demonstrate the key role of CCR5 in the mobilization and colonization of MDSC at the tumor site. Further we show that a soluble CCR5 fusion protein (CCR5-Ig) that we constructed inhibit the accumulation of these cells at the tumor site of WT mice bearing each of these tumors. We believe that CCR5-Ig could be used as a future drug, alone, or in combination with chemotherapy, to cancer diseases.

THE TUMOR AND STROMA IN BREAST CANCER: INFLAMMATION-DRIVEN PRO-CANCER EFFECTS AND THEIR POTENTIAL THERAPEUTIC IMPLICATIONS

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Studies of the last decade have indicated that tumor-associated inflammation is a hallmark of breast malignancy. In our studies we found that high expression of the inflammatory cytokines TNFalpha (=TNFa) and IL-1beta (=IL-1b) by breast tumor cells was significantly associated with disease relapse. Current studies indicate that in contrast to its tumor-cytotoxic effects caused by acute local administration, chronic and persistent presence of TNFa in tumors has strong pro-tumoral effects in many cancers. We have shown that in breast cancer TNFa promoted pro-cancerous functions in the tumor cells and in stroma cells alike, doing so by establishing cooperative functional networks with intrinsic tumoral elements and with microenvironmental factors. TNFa has induced the oncogenic activation of WT-Ras in tumor cells, leading to elevated angiogenicity, and metastatic dissemination of the tumor cells. Also, we identified TNFa as a key inducer of cell remodeling and epithelial-to-mesenchymal transition (EMT) in breast tumor cells, whose cooperativity with other factors prevailing in the microenvironment of luminal breast tumors has led to selection of aggressive and highly metastatic breast tumor cells. In parallel, we found that the joint forces of TNFa and IL-1b could provoke disease recurrence by inducing EMT processes in non-transformed breast epithelial cells, leading to their migration out of acini, collapse of normal breast architecture and potentially re-seeding at the primary tumor site. In parallel, TNFa had a strong impact on stroma cells that prevail in breast tumors. Gene array analyses have identified TNFa targets in these cells, and have shown that direct tumor-stroma contacts are necessary for induction of tumor-promoting activities. Together, our results have identified multi-level and combinatorial tumor-promoting activities of TNFa through which the cytokine potently aggravates disease course in breast cancer, and suggest that anti-TNFa therapies should be clinically introduced for the treatment of breast cancer patients.

DIFFERENTIAL METHYLATION OF P73 VARIANT (DELTANP73) IN NORMAL BREAST EPITHELIUM AND SUSCEPTIBILITY TO BREAST CANCER IN BRCA1/2 MUTATION CARRIERS

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Introduction: Women that carry a heterozygous mutation in BRCA1/2 face an extremely high risk of breast and ovarian cancer but rarely of other cancers. The BRCA1/2 proteins play a role in DNA damage response, essential machinery in all cells. Why disruption of this universal mechanism predisposes to cancer almost exclusively in the breast and ovary is still an enigma.

Hypothesis: We suggest that the unique epigenetic background of the normal mammary epithelium may team up with BRCA haploinsufficiency to confer the marked susceptibility of this tissue to cancer in BRCA mutation carriers. Accordingly, the recognition of the epigenetic make-up of normal tissues may disclose interactive players that influence tissue susceptibility to cancer, and add a novel perspective on carcinogenesis and on tissue protective mechanisms.

Methods: To study breast specific methylation we established genome wide methylation profiles of various normal epithelial tissues and identified 110 genes that were differentially methylated in normal breast epithelium. A number of these genes also showed methylation alterations in breast cancers.

Results: We found that the promoter of deltaNp73, the antiapoptotic and oncogenic variant of p73, was unmethylated and markedly induced by DNA damage in normal human mammary epithelial cells. In contrast, in other normal epithelial cells the deltaNp73 promoter was fully methylated and transcription was not induced.

Implications: This work may point to inherent weakness of the DNA damage induced apoptotic pathway in mammary epithelium that could contribute to its marked susceptibility to cancer on top of genetic instability due to BRCA deficiency.

The findings may provide key insights on neoplastic transformation in hereditary breast cancer and could stimulate novel strategies for prevention and treatment of BRCA1/2 mutation carriers.

SENESCENCE AND THERAPY INDUCED SENESCENCE - ROLE OF PKC

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Senescence refers to permanent cell cycle arrest resulting in long term loss of proliferative capacity, despite continued cell viability and metabolic activity. Senescent cells secrete copious amounts of inflammatory cytokines and immune modulators, down-regulate extracellular matrix proteins, and up-regulate enzymes that degrade extracellular matrix, changes that together are defined as the senescence- associated secretory phenotype (SASP). Thus, although senescence functions as an anti-proliferative program, capable of limiting tumorigenesis, senescent cells can also promote an inflammatory microenvironment that stimulates tumor progression. Here we put forward the novel proposition that Hodgkin's lymphoma (HL) is a malignancy containing senescent cells. HL is a unique malignancy containing high amounts of activated immune cells surrounding a small number of HL tumor cells (1-2% of the cellular infiltrate). The HL tumor cells are composed of Hodgkin (mononucleated) and characteristic Reed-Sternberg (RS) cells (large, sometimes multinucleated). We propose that the large RS cells are in senescence, and as a result, produce large amounts of SASP. We show markers of senescence in RS cells in tumor biopsies. Moreover, we could increase the proportion of large RS cells by chemotherapy drugs. We have previously reported that PKCn (PKCeta) confers resistance against cell death induced by chemotherapy in HL lines and breast cancer. Using PKCn-shRNA and its kinase-activating human polymorphic variant (374I), we demonstrate that it upregulate markers of senescence, including the cell cycle inhibitors p21Cip1 and p27Kip1, and modulates the transcription and secretion of major SASP components. Moreover, it creates a positive loop for reinforcing senescence by increasing the transcription of both IL-6 and IL-6 receptor. As there is now considerable interest in senescence activation/elimination to control tumor progression, it is crucial to reveal the molecular regulators of senescence. This will improve our ability to develop new strategies to harness senescence as a potential cancer therapy in the future.

FROM TARGETED TO MULTI-TARGETED CANCER TREATMENTS

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Malignant tumors are characterized by inherent genomic instability, which leads to ever-changing heterogeneity, limiting the efficacy of targeted therapy. We therefore sought strategies that would hit the heterogeneous tumor at many targets, and would not be confined to cells harboring a specific tumor driver. We began with tumors that overexpress EGFR. This receptor is currently targeted in the clinic by Gefitinib, Erlotinib, Lapatinib, Cetuximab and Panitumumab. These agents exhibit weak efficacies, since non-mutated EGFR is not a survival factor, although it is often overexpressed.

We converted the overexpression of EGFR, rather than its function, into the Achilles heel of the tumor. This was achieved by utilizing EGFR-homing vectors, both chemical vectors and recombinant proteins, that can carry PolyInosine/PolyCytosine (PolyIC). The EGFR overexpressing tumor cells internalize large amounts of PolyIC via the EGFR receptor. In addition to a direct cell killing effect, mediated by PKR and other dsRNA-dependent intracellular signaling proteins, PolyIC induces a bystander effect, due to the production of interferon-alpha/beta and cytokines that recruit NK and T cells. These immune cells, as well as interferon-a/b itself, attack all tumor cells, whether they express EGFR or not, while sparing the more robust non-tumor cells. The EGFR targeting vectors, carrying PolyIC, show excellent anti-tumor activity in animal models.

Since the vector for delivery of PolyIC is modular, the EGFR homing ligand can be replaced by other ligands that home to receptors that are overexpressed on tumor cells. We constructed a Her-2 homing vector, utilizing Her2Affibody as the homing ligand. This vector, with PolyIC, annihilates Her-2 overexpressing breast cancer cells, including trastuzumab/herceptin resistant ones, with promising efficacy in vivo. A vector targeting metastatic prostate cancer surface membrane antigen (PSMA) shows excellent efficacy in cellular experiments and is currently being tested in vivo. This new strategy tackles an important deficiency of targeted therapy, namely its inability to contend with the heterogeneity of malignant tumors.

EXPLOITING GLOBAL EFFORTS ON CANCER GENOMIC MUTATIONS TO OPTIMIZE TREATMENT CHOICE FOR OTHERWISE REFRACTORY CANCER CASES

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The personalized medicine services approach we develop in Bar Ilan faculty of medicine involve a clinical and preclinical service core. Both clinical services (drug indications for each patient) and the pre-clinical (provide pharmaceutical companies with biomarkers to include in the IND to the FDA as inclusion criteria or complex indications, before phase one begins) services rely on cancer target sequencing, patient derived xenografts, and comprehensive biochemical kinome analysis. A specific emphasis is given to combination therapies that could improve efficacy and eliminate resistance. To each patient or investigated drug we provide: (1) Novel approaches for improving the performance and validity of predictive disease markers; (2) Understanding the mechanistic basis of disease markers; (3) Generating novel imaging/molecular imaging approaches for screening and management; (4) Identifying and validating molecular targets for combination therapy. We are also investigating the adaptive immunological repertoire of the patients, with the aim of identifying immunoglobulins or T-cell receptors that assist the battle against the disease, and could become inclusion criteria for immunotherapy.