ABSTRACTS FOR UNFUNDED ISRAEL CANCER ASSOCIATION 2018 CANCER RESEARCH FELLOWSHIPS

Reference Number 20180006 $22,000 in funding requested

Name of Applicant: Prof. Ben Arie-Eran, Lin Medical Center

Patients undergoing surgical procedures for gynecological cancers frequently experience intense anxiety prior to surgery, reflecting the uncertainty regarding diagnosis, treatment and prognosis of their illness. In the present study, we will examine the impact of integrative medicine on the well-being of patients undergoing gynecological cancer related surgery. In addition to receiving standard supportive and palliative care, participants will be offered the addition of complementary medicine such as acupuncture, massage, and meditation, specifically designed for the operating room setting. These therapies will be provided by a team of integrative medicine practitioners trained in both complementary medicine and supportive cancer care. These practitioners will be integrated within the conventional medical team, with acupuncture and related modalities given at three stages – upon entry to the operating room, during the surgery, and at the end of the 240hour post-operative period. Patients scheduled to undergo gynecologic oncology surgery will be randomly allocated (without prior knowledge of the surgeon) to either a treatment group receiving complementary medicine in addition to standard supportive care; or to a control group receiving only standard supportive care. Patients' anxiety, pain and well-being will be assessed for both study groups using validated quality of life questionnaires. In addition to these patient reported outcomes, we will monitor objective parameters for assessing pain severity and the need for anesthesia and pain medication during and following surgery. The proposed research will be conducted by a team of integrative and gynecologic oncologists who have been closely collaborating on a number of research projects over the past decade, through which an integrative model of support and palliative gynecologic cancer care has been evolving. It is our intention to further expand the collaborative research to peri-operative setting., with the goal of improving patents' well -being during this period on the oncology treatment process.

Reference Number 20180012 $22,000 in funding requested
Name of Applicant: Dr. Barak Rotblat, Ben-Gurion University of the Negev

Cancer is a heterogeneous disease and patients who carry seemingly similar tumors may respond very differently to therapy. To improve patient outcome, we must better understand cancer at the molecular level; today, sequencing technologies are available for diagnostic purposes and novel gene manipulation technologies are getting closer to clinical applications. In the past few years, it has become clear that, in addition to the 20,000 genes whose products are RNAs that are translated into proteins, our genome harbors some 50,000 genes whose product are RNAs that are not translated into proteins and are known as long noncoding RNAs (lncRNAs). Currently, although it is clear that lncRNAs participate in all aspects of cell biology, we know the function of only a small fraction of these lncRNAs. By interrogating patient-derived data, we have already identified 55 lncRNAs whose expression in the tumor is associated with low survival rates. However, we have not yet identified the functions of these genes in the tumor cells. We propose to use a simple – yet elegant – approach to interrogating all these genes in parallel, using patient-derived glioblastoma tumor cells, and to identify those that promote tumor cell survival or growth. This study will bring forth lncRNAs as a new promising diagnostic tool and as drug targets in glioblastoma. We envision that our approach will be applicable for studying lncRNAs also in other types of cancer and cancer traits, such as drug resistance and metastasis

Reference Number 20180025 $22,000 in funding requested
Name of Applicant, Dr. Menachm Gross, Hadassah Medical Center Ein Kerem Campus

Background: restoration following total laryngectomy in patient with laryngeal cancer. However, VP has the propensity to become rapidly infected by micro-organisms such as fungi and bacteria that form biofilm. VP failure due to biofilm causes esophageal contents to leak into the trachea, resulting in VP deterioration and failure of the device, aspiration pneumonia, compromised speech, and repeated prosthesis replacement with short VP lifespan. **Objective:** To develop a novel means of prevention of biofilm formation on VP. The concept is to coat the VP with a sustained release varnish coat embedded with chlorhexidine which will prevent potential microbial infections and biofilms, and thereby improve voice quality, increase quality of life of post-laryngectomy cancer patients, and increase the interval of VP replacement.

Reference Number 20180029 $52,000 in funding requested

Name of Applicant, Dr Orna Steinberg-Shemer, Schneider Children's Medical Center

Severe congenital neutropenia (SCN) is a genetic disease in which the production of neutrophils, a type of white blood cell essential for the immune system, is impaired, thus causing early onset life threatening infections. Treatment with granulocyte-colony stimulating factor (G-CSF) prevents these severe infections. However, the resulting prolongation of the life-span of patients with SCN revealed the development of leukemia in many of them. Leukemia development depends on the dose of G-CSF treatment, and in many cases is preceded by the appearance of mutations in the receptor for G-CSF. The mechanisms causing leukemia, and the role of G-CSF treatment and of mutations in the G-CCSF receptor in this process are not well understood. Induced pluripotent stem cells (iPSCs) are cells produced by reprograming adult cells. iPSCs can differentiate into all cell types. Therefore, iPSCs have enormous potential for clinical and research applications, including generation of disease models, drug screening, and regenerative medicine. We generated iPSCs from SCN patients, and we aim to introduce in these cells mutations in the G-CSF receptor, in order to generate a model for leukemia development in SCN. We will study the effect of the G-CSF receptor mutations on the differentiation to white blood cell precursors and on gene expression. We will also examine the capability of different drugs to inhibit the effect of such mutations. Thus, our study can help develop strategies to reduce the risk for malignancy in SCN patients. Furthermore, it may increase our understanding of similar processes not related to SCN, and thus have a broad impact on our knowledge of cancer development and our ability to prevent it.

Reference Number 20180045 $52,000 in funding requested

Name of Applicant, Dr. Tal Burstein-Cohen, The Hebrew University of Jerusalem

Immune cells that are initially recruited to fight cancer paradoxically often contribute to tumor growth and enhanced metastasis posing a significant challenge in the clinic. Assuming the role for PROS1– a protein secreted by immune cells – we assumed I that inhibiting PROS1 in immune cells will slow down tumor growth and metastasis. However, we unex0pectedly discovered that inhibiting PROS1 exacerbated cancer progression, revealing its novel anti-tumor role. Here we propose to thoroughly investigate how PROS1 mediates its anti-tumor properties, and to test whether it may be further developed as an anti-cancer therapy. To test this we developed a special strain of mice lacking PROS1 expression in a certain subset of immune cells. We challenge these mice and control mice with tumor cells and compare primary tumor and metastasis progression. Because immune cells paradoxically contribute to growth of many tumors, we believe our findings are relevant to many cancers types, and our findings may help fight a wide variety of cancers. This is a first study to evaluate PROS1 as an anti-tumor agent and our preliminary results inspire PROS1 as a logic potential candidate for therapy aimed at inhibiting cancer and metastatic growth.

Reference Number 20180047 $22,000 in funding requested

Name of Applicant: Dr. Zvi Granot, The Hebrew University of Jerusalem

Neutrophils are the most abundant population on white blood cells in the human circulation. Although their function is usually associated with fighting microbial infections they were also found to play important roles in cancer. Neutrophils are not a homogenous population of cells and consist of both anti-tumor and tumor promoting subsets. Our previous observations identified TGFbeta, a highly potent molecule whose expression is dramatically increased in cancer, as a key regulator of neutrophil activity in cancer. TGFbeta promotes tumor growth by both enhancing the proportion of tumor-promoting neutrophils and blocking the anti-tumor neutrophil activity. Here we propose to study the molecular mechanism through which TGFbeta exerts its tumor promoting effect on neutrophils. We will associate specific cancer related neutrophil traits with specific TGFbeta response pathways and use mouse models of cancer to test how perturbing these pathways in neutrophils affects tumor growth and metastatic progression. The successful completion of the proposed study will enhance our understanding of neutrophil function in cancer. More importantly, is will highlight specific TGFbeta response pathways that may be targeted therapeutically to enhance neutrophil anti-cancer responses. This may serve as a novel immune approach to treat cancer and will take us a step closer to curing cancer.

Reference Number 20180054 $22,000 in funding requested

Name of Applicant: Dr. Ilan Bruchim, Tel Aviv Sourasky Medical Center

Women with suspected early stage cancer of gynecological origin undergo surgery to determine further treatment. Tissue sample is excised & the type of tumor is determined using histopathological tests. Accurate histological results are received only days after the biopsy & iy may determine of additional hospitalization and surgery is required. On the day of the first biopsy, some frozen section tests are available within 45 minutes, but these results come with reduced accuracy, which may be as low as 75%. On receiving these results, surgeons may perform or avoid the full surgical procedure with increased risk of misdiagnosing malignancy. Recent studies have shown that infra-red spectroscopy of excised tissue can be differentiated between malignant and benign tumors very rapidly.. Small tissue samples from excised biopsies are placed on the spectrophotometer and measured. We plan to perform infra-red spectroscopy measurement of the tissue from the excised biopsy in tandem with the 'frozen section test. The accuracy of each test will be assessed individually and as a combined measure of malignancy' We belief that the use of the infra-red spectroscopy will ead to a decreaswe in the number of misdiagnosed tumors.

Reference Number 20180055 $22,000 in funding requested.
Name of Applicant: Dr. Liza-Barki Harington, University of Haifa
Multiple myeloma (MM) is an incurable form of bone marrow cancer. Despite significant advances that prolong patient survival, the disease inevitably relapses, thus demanding identification of additional therapeutic targets for advances lines of therapy. We propose that COX-2, an inflammatory enzyme whose overrepresentation in MM tumors predicts a poor outcome, increases cell division in a new mechanism that does not involve its classic enzymatic activity. Rather, we find that cleavage by COX-2 by a protein called SK-1 generates smaller COX-2 fragments that localize to the cell nucleus and affect the ability of cells to propagate or die. We further show that treatment of cell lines originating from MM tumors with an inhibitor of SK-1 significantly slows down their growth. Based on these findings, the hypothesis of this proposal is that cleavage of COX-2 by SK-1 enhances the ability of the MM cells to divide and therefore we may be able to treat MM by inhibiting the protein that cuts COX-2. The aims of the proposal are to measure the presence of truncated COX-2 fragments in MM-derived cell lines and in bone marrow of MM patients at diagnosis and different stages of disease, to identify cellular pathways that are affected by COX-2 cleavage and the determine the effect of SK-1 inhibitor with or without clinically available used drugs on MM proliferation. **Since over-representation of COX-2 is characteristic of many other types of cancer, we believe that findings from this study will impact not only MM, but also additional neoplasms and provide a new line of drugs as a means of fighting cancer.**

Reference Number 20180062 $22,000 in funding requested
Name of Applicant: Dr. Yoav Shaul, The Hebrew University of Jerusalem
In Israel, breast cancer accounts for 33% of all new annual cases of cancer in women. Despite a major progress in the understanding of this disease, many breast cancer patient do not survive. One of the major cause for high mortality rate is the formation of metastatic niches in other organs such as the lung. At the early stages of disease, the tumors look relatively similar to the breast tissue and are sensitive to drug treatments. As time passes, however, they become more aggressive, adopt properties that differ substantially from the surrounding tissue, become less sensitive to drugs, and become metastatic. Previously, I have developed computer based model and experimental setting whereby I detect metabolic enzymes that play a key role in the ability of cancer to form metastasis. One of the genes that we identified to potentially play a key role in metastasis is GPX8 that its cancer related function is still unknown**. My principal aim in this proposal is to formulate protocols to understand the role of an enzyme named GPX8 in metastatic formation.** The advantage on working with enzyme that they are relatively easier to be inhibit by drugs. This work therefore has the potential to not only advance our understanding of tumor aggressiveness and its metabolic regulation, but also to identify a new class of anticancer drugs that target the metabolic roots of tumor aggressiveness.

Reference Number 20180075 $22,000 in funding requested
Name of Applicant: Dr Rostislav Novak, Rambam Healthcare Campus

Osteosarcoma (OS) is a devastating childhood cancer for which current therapy is of limited value. Thus, the identification of molecular targets for precise intervention in OS is necessary. Of specific interest are the genes essential for the survival of OS cancer cells, but not for normal bone cells. The "Non-Oncogenic Addiction genes (NOA) are essential for the survival of cancer cells and enhance their tumorigenicity. Thus they are potentially valuable for targeted therapy in OS. This study will focus on a potent NOA gene ubiquitin ligase termed RNF4 enhancing tumor cell growth and chemo-resistance of OS cells.

Reference Number 20180077 $22,000 in funding requested
Name of Applicant: Prof. Zelig Ashhar, Tel Aviv Sourasky Medical Center

Many of the anti-cancer treatments that have been developed in the last decade are based on the immune system. **The purpose of these treatments, collectively called cancer immunotherapy, is to specifically eradicate tumors using modified immune components that elicit targeted and empowered anti-cancer response.** Our research is engaged with the development of immunotherapy based on a special subset of white immune cell, called T cells, genetically modified to express a synthetic (CAR) that redirect them to reject cancer cells. T cells that expressed CARs can interact with targets on the surface of tumor cells and induce their killing. The CAR technology has been extensively evolved since it was first developed in our laboratory by professor Eshhar and his colleagues. As for today, CAR T cells have already entered clinical testing in patients in a few leading clinical centers for the treatment of certain hematological caner types. These trials have shown a remarkable outcome in several B-cell lymphomas and leukemia in adults and in children. In this application **we propose an anti multiple-myeloma (MM) treatment that combines CAR-based therapy and neutralization of an immune-suppressive environment that the tumor induces. Suppressive immune pathways limit and counteract the anti-cancer function of immunotherapy. We propose in this pre-clinical study to determine whether combining CAR T cells therapy and blockade of inhibitory pathways would have a synergistic anti-MM effect.** Each of these approaches has been used singly in the clinic however, many patients do not respond to either treatment alone. **We expect that a combined treatment can improve CAR T cell-based immunotherapy, providing effective and durable benefit to MM patients**. Multiple-myeloma is the second most frequent hematological malignancy. In Israel, 350 new patients are diagnosed every year. Most patients are diagnosed around the age of 65 however the number of patients diagnosed at younger ages is growing world widely. Although multiple therapeutic alternatives are currently available, multiple-myeloma is still an incurable disease with a mean survival of 10 years.

Reference Number 20180087 $52,000 in funding requested

Name of Applicant Dr. Nissan Yissachar, Bar- Ilan University

Chemotherapy causes many side effects, most commonly mucositis - chronic inflammation of the digestive tract. Mucositis affects almost all patients undergoing chemotherapy and bone marrow transplantation. In addition to being severely painful and increasing the risk for infections, mucositis becomes a dose-limiting factor, thus worsening recovery. Chemotherapy disrupts the delicate balance between the natural gut bacteria and the immune system, which triggers and promotes mucositis. However, the mechanisms by which chemotherapy interfere with these communications are mostly unknown. We now propose to bypass the limitations of live animal models and to utilize a novel experimental system for gut organ cultures, which we have recently developed, **to understand how chemotherapies disrupt the healthy communication between gut bacteria and the immune system. Understanding these interactions may promote new therapeutic approaches to restore the balance between gut bacteria and the immune system during chemotherapy, reduce side effects, and boost anti-cancer therapy.**

Reference Number 20180098 $22,000 in funding requested

Name of Applicant Dr Yafit Gilboa, The Hebrew University of Jerusalem

Cancer survival rates have increased dramatically in recent years. However, many **survivors report cognitive decline, affecting their daily function and their quality of life. Computerized cognitive training** programs have been found effective in improving cognitive function such as memory and attention. However, most studies report limited improvement in everyday function following training. A complementary **treatment approach delivered by occupational therapists directly targeting daily function** has shown recent promise. Here, we propose that a **combined treatment approach**, comprised of both methods, would be effective due to the improved cognitive function resulting from cognitive training and the improved daily function due to the functional treatment. An added value of the combined treatment approach is its remote delivery, using online training protocols, making them an accessible, cost-effective treatment option. The proposed study will include 75 cancer survivors, randomly assigned to one of three groups. The first group will receive the combined treatment, the second will receive computerized training only, and the third will continue with treatment-as-usual. Immediate and enduring effects of treatment will be determined by examining effects at the completion of the 10-week intervention period and following 3 months. **Positive results in the proposed study could potentially change the therapeutic landscape for treatment of cancer-related cognitive decline, which currently impair the lives of millions worldwide.**

Reference Number 20180101 $22,000 in funding requested

Name of Applicant: Dr. Iris Lavon, Hadassah Medical Center

Glioblastoma multiforme (GBM) is an extremely aggressive brain tumor and despite the extensive efforts made so far, the median survival time is still very poor (14.6 months); in part due to a lack of good therapeutic options. Although under the microscope all glioblastoma look very similar and currently treated, at least at the initial treatment stage, with the same treatment regimen, the genetic characteristic of these tumors can vary considerably. Thus, **the identification of new molecular therapeutic targets remain an unmet need.** To address this unmet need **we performed a genome-wide array on DNA extracted from GBM samples obtained from 5 women and found that androgen receptor (AR) is amplified in 4/5 samples. Further analysis on more samples from patients of both sexes revealed that the majority of GBM express AR also at the RNA and protein level.** This finding was very surprising, since AR is a nuclear receptor activated by binding to the androgenic hormones and primarily responsible for the development of male sexual characteristics. However, based on its involvement in prostate and breast cancer amenable to treatment with AR antagonists, such as enzalutamide and bicalutamide, we tested in vitro three glioma cell lines with these agents. This treatment yielded dose-dependent cell cytotoxicity in all cell lines. Furthermore, we found that 30% of GBM express an AR variant that does not respond to its normal ligand and is involved in induction of AR via other signal transduction, such as the epithelial growth factor receptor (EGFR) pathway. Combination therapy with anti-AR agent with an EGFR inhibitor in cell lines bearing such an AR splice variant yielded a better efficacy than an AR-antagonists alone. Enzalutamide given orally to nude mice bearing a human glioma resulted in a 72% reduction in tumor volume ($p=0.0027$). **The objective of the suggested study is to elucidate the signaling pathway in which AR contributes to cancer growth in glioblastoma.** A clear and comprehensive understanding of the mechanism of AR signaling in GBM may lead to a new approach for the treatment of this devastating disease.

Reference Number 20180113 $22,000 in funding requested
Name of Applicant Prof Rivka Dikstein, The Weizmann Institute of Science
Normal life of human cells greatly depends upon balanced expression of thousands of genes. It is very well established that upon development of cancerous processes (such as tumorigenesis and metastasis), expression of multiple genes is impaired and becomes imbalanced. Such dysreguation of genetic expression is thought to be one of the major driving forces that allow cancerous cells to escape the immune system, proliferate and create metastases. Stability of messenger RNAs (mRNAs) is one of the central mechanisms that protect cells from imbalanced expression of genes. Majority of mammalian mRNAs is relatively short-lived (approximately 5 hours), but many are extremely unstable (with lifespan of less than one hour), while others can exist for days. While some of the reasons underlying such dramatic differences in the mRNA turnover are described, it is generally not well understood which factors determine the stability of most transcripts. In this joint research proposal we anticipate to achieve a better understanding of general mechanism that imprints mammalian mRNAs upon their birth (e.i. transcription), via an epigenetic level of stability control. Our preliminary data suggest that mRNAs that possess low rate of transcription tend to rapidly degrade, while mRNAs that are transcribed very efficiently tend to be more stable. We propose an epigenetic mechanism that explains how transcription can mediate mRNA degradation, despite these processes being separated in space and time. Our study will shed light on one of the mechanisms that mediate balanced expression of genes. Collaboration with the Agami group from the Netherlands Cancer Institute will allow us to expand our observations to the majority of mammalian genes, investigate in depth the mechanism that couples between transcription of mRNAs and their stability and better understand diseases that stem from imbalanced gene expression, such as cancer.

Reference Number 20180115
Name of Applicant: Dr Tzafrir Zor, Tel Aviv University
Inflammation is a hallmark of cancer. Pro-inflammatory mediators released from immune cells stimulate expression of genes involved in survival, proliferation, migration, invasion and metastasis of cancer cells. TLR4 is a receptor, present on immune cells, that senses infection with Gram-negative bacteria by recognizing a pathogen-associated molecular pattern (PAMP). Sterile Inflammation, namely – inflammation in the absence of a pathogen, is involved in cancer progression. The trigger for sterile inflammation is considered to be a danger-associated molecular pattern (DAMP), an endogenous factor which mimics the PAMP by activating the same receptor. Our preliminary results indicate that the lipid ceramide-1- phosphate (C1P) is a DAMP that initiates sterile inflammation via TLR4. Interestingly, TLR4 is over-expressed also on cancer cells and promotes their proliferation, migration, invasion and metastasis, while C1P is present extracellularly in blood and tissues and can stimulate the same activities of cancer cells. Thus, we propose to determine whether C1P stimulates key steps in carcinogenesis via TLR4. The expected findings would yield new drug targets and therefore may have implications for cancer therapy.

Reference Number: 20180118,$22,000 in funding requested
Name of Applicant: Dr. Lena Ilan, Rambam Healthcare Campus

In 2015, cancer caused over 8.7 million deaths globally and was the second leading cause of death behind cardiovascular diseases. One of the greatest challenges in cancer treatment is the cancer cells' plasticity and their ability to use redundant pathways to reach constant activation of molecular pathways that enable cell growth and propagation. **The aim of this project is to identify the key interactions between the two main cancer regulatory pathways and to disrupt these interactions in a way that a cancer cell could not bypass the inhibition of the aberrantly activated pathways. It will potentially ablate the cell growth and provide a tool for treatment development.** In our preliminary research, we found a novel interaction between the two major regulatory pathways crucial for cancer development, namely glycolysis and mTOR. These two pathways altered in most if not all cancer types, indicating their vitality for every cancer cell. Our objective is to elucidate the mechanism of this interaction and to identify possible leverage points for development of effective treatment for a wide range of cancer types

Reference Number 20180116 $22,000 in funding requested
Name of Applicant: Dr, Michal Braun, The Academic College. Tel Aviv-Yaffo

The goal of the proposed study is to estimate levels and prevalence of compassion fatigue and compassion satisfaction among oncologists In Israel. Compassion fatigue is defined as a state of tension and preoccupation with traumatized and suffering patients (Figley, 1995; 2002). It is resulted in reduced capacity and interest in being empathetic for a suffering individual (Adams et al., 2006). To the best of our knowledge, no study was conducted on compassion fatigue among oncologists, although they might be especially prone to it due to their exposure to profound amount of human suffering, pain, loss and death. Compassion satisfaction is the positive benefits that helping professionals derive from working with traumatized, suffering people, and their levels of satisfaction from that work (Stamm, 2002). Moreover, the proposed research focuses on three clusters of variables that might play a mediating role in the association between exposure to suffering and death and compassion fatigue/compassion satisfaction: predispositions (locus of control, attachment orientation and empathy), situational psychological responses (Sense of failure, Guilt, Learned Haplessness and Grief) and demographic variables

Reference Number 20180022 $22,000 in funding requested

Name of Applicant: Dr. Dan Levy, Ben-Gurion University of the Negev

Cancer treatment is currently shifting toward more personalized approaches whose successful application requires knowledge of the global differences in the expression patterns of specific cancer markers. Accordingly, there is a critical need for technologies capable of proteome-wide analyses to identify such bio-markers. In the proposed research, we will employ cutting edge experimental approaches to identify novel biomarkers that modulate breast cancer, focusing on the novel protein SETD6, which belongs to a family of enzymes that have already been linked to the regulation of neoplastic diseases. We have str9ong preliminary data suggesting that SETD6 is involved in a process termed EMT (epithelial -to-mesenchymal transition) in which normal epithelial cells acquire cancerous mesenchymal cell properties, leading to enhanced aggressiveness, higher proliferation rate and invasiveness that enable them to invade and metastasize. We will test the specific hypothesis that SETD6 modulates the progression of the EMT process in breast cancer. The proposed research will potentially have broad implications for basic and translational research and promote the identification of new therapeutic targets or alternative strategies for cancer.