ICRF Researchers Explore New Pathway to Treat Colorectal Cancer and Pulmonary Fibrosis

A team of researchers led by Ariel Munitz, Ph.D., of the Department of Clinical Microbiology and Immunology at Tel Aviv University, may have found a new way to limit the progression of colorectal cancer, the second leading cause of cancer-related deaths in the United States and the third most common cancer in men and in women. More than 136,700 people in the U.S. were diagnosed with colorectal cancer in 2009 (the last year for which statistics are available) and 51,848 people in the U.S. died from the disease.

Munitz and his team are focusing their attention on macrophages, large white blood cells that are part of the body's immune system. When a foreign invader such as bacteria enters your blood stream, macrophages secrete certain substances to help kill the bacteria. Sometimes, however, activation of macrophages has damaging effects, including tumor progression. Research has shown that certain immunoglobulin-like receptors—cell surface proteins found on important cells of the immune system—can inhibit macrophage activation. Munitz and his colleagues are studying the effects of a cell-surface molecule called paired immunoglobulin-like receptor B (PIR-B) on macrophage activation in colorectal cancer.

The research is funded by a grant from the Israel Cancer Research Fund (ICRF), a nationwide charitable organization founded in 1975 by a group of American and Canadian researchers, oncologists, and lay people determined to harness Israel's educational and scientific resources in the fight against cancer. ICRF is the largest U.S.-based charity solely devoted to supporting cancer research in Israel and receives its total income from private donations.

The current ICRF grant has enabled Dr. Munitz and his team to identify that PIR-B suppresses the activities of so-called “tumor-associated macrophages”. While ongoing studies in Munitz's group are now focused on understanding how this affects colorectal cancer progression, a team of researchers in Israel and Germany, led by Munitz, has recently shown that PIR-B can limit the devastating effects of idiopathic pulmonary fibrosis (IPF), a progressive lung disease that affects between 132,000–200,000 people in the U.S. Pulmonary fibrosis occurs when lung tissue becomes damaged and scarred, making breathing more difficult. In most cases, doctors can’t pinpoint a cause, thus the condition is termed idiopathic. As the disease worsens, people with IPF become progressively more short of breath. Approximately 50,000 new cases of IPF are diagnosed in the U.S. each year, and as many as 40,000 Americans will die from the disease. Current estimates suggest that the number of individuals diagnosed with IPF is growing and will continue to increase in the U.S. and worldwide.

Lung damage caused by the disease can’t be repaired, but medications and therapies, including lung transplantation in selected patients, can sometimes help ease symptoms and improve quality of life. “IPF is a major cause of morbidity and mortality, with no effective treatment,” explained Munitz.

Dr. Ariel Munitz is a Senior Lecturer in the Department of Clinical Microbiology and Immunology at the Sackler Medical School of the Tel Aviv University and an Adjunct Assistant Professor in the Division of Allergy and Immunology at the Cincinnati Children’s Hospital Medical Center Cincinnati, OH.

Dr. Munitz received a B.Sc. in Medical Sciences at the Hebrew University. He then earned a Ph.D. in the Department of Pharmacology, and later spent three years conducting research at Cincinnati Children’s Hospital Medical Center in Ohio.

Born in Jerusalem, Dr. Munitz still lives there with his wife, Kineret, and their three children.

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ICRF Researchers Take Aim at Pancreatic Cancer

Discoveries by ICRF Researchers Point to New Therapy for Brain Cancer

ICRF Researcher Targets Malignant Melanoma
Each year approximately 22,000 people in the United States are diagnosed with a potentially life-threatening brain tumor. Until recently, treatment options have been limited. Glioblastoma—the most common and aggressive type of brain cancer in adults—tends to spread rapidly through the brain tissue. Because the brain is enclosed in the skull and the skull cannot expand to make room for a growing tumor, a tumor can press on or damage brain tissue. As with many tumor types, the exact cause of glioblastoma is unknown. Glioblastoma tumors are extremely difficult to remove by surgery. Median survival for patients with glioblastoma who are treated with chemotherapy and radiation is about 14.6 months, and only about 10% of patients remain alive five years or longer after diagnosis. Thus, enrollment in a clinical trial—a last resort for patients with more treatable types of cancer—is often recommended by cancer specialists as the best treatment option.

But research supported by the Israel Cancer Research Fund (ICRF) is discovering previously unknown molecular aspects of brain cancer, providing new opportunities for diagnosis and treatment. Led by Regina Golan-Gerstl, Ph.D., a Postdoctoral Fellow in the laboratory of Rotem Karni, Ph.D. of the Department of Biochemistry and Molecular Biology, Institute for Medical Research Israel-Canada, Hebrew University-Hadassah Medical School, investigators have identified a genetic protein (splicing factor hnRNP A2/B1) likely to be involved in the development and spread of glioblastoma.
The ICRF researchers analyzed tumor samples from patients with various types of brain cancer and compared them with samples taken from normal brains. They found that hnRNP A2/B1 was highly “overexpressed” (that is, higher than normal levels were detected) in the glioblastoma samples. In further studies, laboratory mice injected with glioblastoma cells quickly developed large tumors. But when investigators used a biologic technique (“knockdown”) to reduce hnRNP A2/B1 before injection, the mice developed only small tumors or no tumors at all.

“These results suggest that hnRNP A2/B1 is a driving oncogene (a gene that causes normal cells to become cancerous) on its own and probably directly contributes to glioblastoma development,” says Dr. Karni. “Moreover, overexpression and amplification of hnRNP A2/B1 correlate with poor prognosis of glioma patients, whereas deletion of the hnRNP A2/B1 gene correlates with better prognosis than average.”

Dr. Karni and his team are also trying to identify the genes which are regulated by hnRNP A2/B1. He notes that in a previous study of brain and breast cancer cells with knockdown of hnRNP A2, “we identified key genes of very important pathways involved in cancer development and maintenance,” as well as genes that indicate proliferation of cancer or tumor suppression.

“Taken together, our data suggest that hnRNP A2/B1 is a new biomarker for glioblastoma patient survival and a new proto-oncogene that regulates the splicing and other RNA processing steps of several tumor suppressors and oncogenes,” says Karni. “Furthermore, downregulating hnRNP A2/B1 levels in glioblastoma cells should be considered as a new strategy for glioblastoma therapy.”

Previous findings were reported in the July 1, 2011, issue of the journal Cancer Research, published by the American Association for Cancer Research.

innermost connective tissue that surrounds individual nerve fibres in a bundle) act as a first line of defense in response to nerve injury and inflammation—until they are overrun by blood-borne tumor-associated macrophages originating in bone marrow.

Based on their findings, the research team developed a central hypothesis that endoneurial macrophages “play a key role in the progression and dissemination” of pancreatic cancer, said Gil. Although there has been intensive investigation on the role of tumor-associated macrophages in other cancer types, this is the first time it has been explored specifically with regard to nerve invasion in pancreatic cancer. “Our long-term goal is to understand the mechanism that triggers progression of pancreatic cancer and to develop the means to inhibit it,” he explained.

“It is anticipated that the data obtained here….will provide meaningful advancement of current knowledge in the field of cancer biology and for the benefit of cancer patients,” he concluded. “It is also expected that the results will be equally applicable to other neuroinvasive cancers, including head and neck, gastrointestinal, hepatobiliary, genitourinary, and prostate malignancies.”
ICRF Researcher Targets Malignant Melanoma

Promising new approaches to prevention, diagnosis, and treatment of malignant melanoma are currently being explored in the laboratory of Dr. Carmit Levy of the Department of Human Molecular Genetics and Biochemistry at Tel Aviv University in Israel. The cutting-edge research is supported by a grant from Israel Cancer Research Fund (ICRF). “We very much appreciate the support of the ICRF,” says Levy. “Without it, I would not have been able to establish my new lab in Israel and generate valuable data that will be published soon.” (The data was recently published online, ahead of print, by the Journal of Investigative Dermatology (J Invest Dermatol. 2013 Aug 9, doi:10.1038/jid:2013.340.)

Melanoma, the most lethal form of skin cancer, is responsible for approximately 80 percent of skin cancer deaths. Melanoma occurs in both younger and older people, although rates increase with age and are highest among those in their 80s. But it is also one of the more common cancers in young adults, especially young women.

Despite improved sunscreens, preventive educational efforts and recent advances in treatment options, the incidence of melanoma has risen over the past three decades in the United States more than that of any other cancer. In 2010, it was predicted that one in 50 patients in the U.S. would be diagnosed with melanoma by 2015. That number was already reached in 2012. According to the American Cancer Society, about 76,690 new melanomas will be diagnosed (45,060 in men and 31,630 in women) in 2013 and about 9,480 people (6,280 men and 3,200 women) will die from the disease.

Melanoma originates from a skin cell named melanocyte. Under normal conditions, melanocytes produce the pigment melanin and spreads it to other skin cells. Malignant transformation of melanocyte results in melanoma. Levy has previously studied the role of microRNAs (miRNAs)—small non-protein coding genes—in the development of melanocytes and their role in progression to melanoma. She found that a particular miRNA, miR-211, is down-regulated (decreases) in invasive melanoma cells, and that re-introducing it to those cells blocked their ability to spread, or metastasize.

In the present ICRF-funded study, Levy and her colleagues demonstrate that miR-211 contributes to melanoma adhesion (binding to another cell) by directly targeting a specific gene (NUAK1). Inhibition of miR-211 increased NUAK1 expression and decreased melanoma adhesion, whereas upregulation of miR-211 restored adhesion by repressing NUAK1. Thus, she concluded, “we have identified NUAK1 as a potential target for the treatment of metastatic melanoma. Following our publication, I got an invitation from a researcher in Scotland to collaborate and try drugs he had developed to target the NUAK1 pathway. We are excited by the therapeutic opportunity, although much more needs to be done,” commented Levy.

Carmit Levy, Ph.D.

Dr. Carmit Levy is a Senior Lecturer, Department of Human Genetics and Biochemistry, Sackler School of Medicine, Tel Aviv University, Israel.

Born in Jerusalem, Levy established her lab at Tel Aviv University in 2011, after completing post-doctoral studies at Harvard Medical School in Boston. She began her academic career at the Hebrew University, Jerusalem, where she received a B.A. in biology, followed by a M.Sc. in pharmacology, and her Ph.D. in Biochemistry, again at Hebrew University.

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“Therefore, a better understanding of the pathways capable of regulating fibrogenesis is critical for the development of efficacious therapies for this unmet medical need.”

Macrophages that reside in the lung, for example, known as alternative activated macrophages (aaMacs) have been shown to play a key role in the development of IPF. “Surprisingly,” said Munitz, “pathways that inhibit macrophage functions, especially in IPF, receive little attention.”

The researchers used a mouse model as well as human biopsies taken from patients with IPF to demonstrate that PIR-B can inhibit macrophages known to be active in IPF.

“The cell-surface molecule PIR-B can suppress macrophage activation,” said Munitz. Findings were reported in the American Journal of Respiratory Cell and Molecular Biology. Although the findings are preliminary and “the relative contributions of this family of molecules to the disease remain to be determined,” the results “suggest that strategies aimed at suppressing aaMac functions in IPF may provide new tools to limit the devastating outcomes of this disease,” Muniz concluded. Given the strong correlation between tissue fibrosis, repair processes and cancer progression, the researchers hope to see similar results with regard to colon cancer.