Memorial Sloan Kettering
Cancer Center

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Andrew B. Abramson
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Dear Andy and Colleagues:

It is with great pleasure that I am able to report that considerable progress has been made this year because of the continued generous support of the Cure Breast Cancer Foundation. Our mission is to explore our novel approach to understanding cancer based on our discovery that it is the **mobility** of breast cancer cells that underlies many of their most dangerous characteristics. It is well-known that the ability of cancer cells to spread to vital organs (a process called *metastasis*) is the major life-threatening aspect of cancer. With our colleagues we discovered that cancer cells could, in addition to seeding distant sites, also return back to the cancerous masses from which they came—called *self-seeding*—thereby invigorating tumor growth by interacting with white blood cells, blood vessel cells, and other cells in the vicinity of the mass. Our goal is to examine all aspects of these processes so as to better diagnose, treat, and even prevent breast (and all) cancers.

A major advance is this regard is the discovery (by Drs Elizabeth Comen, Maria Kleppe, Ross Levine and colleagues) that many of the white blood cells (leucocytes) that infiltrate breast cancers themselves have known cancer-causing mutations. This was recently published and presented at the American Society of Clinical Oncology Annual meeting in Chicago. We are developing laboratory models to examine the function of these mutant leucocytes and actively collecting tissue for analysis from certain highly-informative special cases: cancers in women with BRCA1/2 mutations, cancers in women who develop leukemia after breast cancer treatment, and secondary cancers other than breast cancer in women treated successfully for an earlier primary breast cancer. We are also looking at the leucocytes that are infiltrating metastatic lesions. All of this work is intended to lead us to new ways of approaching cancer by focusing on the leucocytes as well as the cancer cells themselves.

Our collaborations with the bio-physicists Drs. Peter Kuhn and Paul Newton, examining the patterns of spread of breast cancers, has now been brought together with our work on the evolution of DNA changes that occur as cancer metastasize and self-seed. With Dr. Jorge Reis-Filho at Memorial Hospital and international colleagues we are examining these changes at great depth so that we can better understand exactly how mutations and other DNA, RNA and protein aberrations can underlie these phenomena.

With Dr. Ethel Siris and colleagues at Columbia University Medical Center and at Soroka University Medical Center in Beer Sheva, Israel, we have found that women who developed breast cancer had on average higher levels of bone mineral density (BMD) than women who did not. However, their risk of having an osteoporotic fracture was significantly higher as compared with women without breast cancer. This means that having had breast cancer makes bones weaker without necessarily lessening the amount of calcium in the bones, which is the common method of assessing bone strength. We are continuing our prospective study comparing BMD values, bone health data and appropriate blood tests from newly diagnosed breast cancer patients and other women without breast cancer. To date 346 patients with newly diagnosed breast cancer have been enrolled with a target enrollment of 400 such patients, and enrollment of controls is following (to obtain well matched women) with a current enrollment of 185 women. As noted previously this was a major topic in an international symposium that the CBCF supported last year at Soroka Hospital, which received considerable press attention in Israel and in the United States.

With Drs. Richard Kolesnick and Philip Paty at the Memorial Sloan Kettering Institute we are studying the role of stem cells in colon cancer, which is closely related to our breast cancer work. We have found that pre-malignant polyps of the colon in mice develop due to a massive expansion of stem cells. We have validated this finding in human tumors, demonstrating that colon polyps and colon cancers are indeed diseases caused by dysregulated growth of colon stem cells. This is critically important in that one of the key characteristics of stem cells is their ability to migrate, the essence of seeding. Cancerous stem cells suppress normal, non-mutated stem cells by a toxic molecule that disrupts the physical contact of stem cells with their neighboring cells. This has therapeutic implications in that disrupting these toxins could be useful not only to treat breast cancer but to prevent it. We are now able to grow cancer stem cells from surgical specimens to see how they respond to radiation therapy. So far we are discovering that the sensitivity of cells to radiation depends on their interactions with their immediate environment, including non-cancer cells. This data might be used to selectively enhance radiation killing of cancer stem cells while not affecting normal intestinal stem cells.

With Dr Rachel Hazan at the Albert Einstein College of Medicine we are studying an important molecule called p21CIP1, which controls cells division as well as cell mobility. Disrupting p21CIP1 stops both metastasis and self-seeding by killing or interfering with the function of cancer stem cells. Augmenting p21CIP1 promotes cancer stem cells, making cancers behave in a more aggressive fashion. This year we plan to determine the molecular pathways by which p21CIP1 works, with special attention to Wnt abnormalities, one of the most common defects in cancers. All of this is intended to lead to interventions that could stop metastasis and all forms of cancer seeding.

In addition, with CBCF support we plan to hold a think tank in Soroka Hospital in October that brings together the world leaders in breast cancer hereditary genetics. The topic will be: Should all Ashkenazi Jewish people be routinely tested for BRCA1 and BRCA2 abnormalities at age 30? Right now we are only testing people with strong family histories of early-onset breast or ovarian cancer, but many people do not know their family histories and many families are too small—or have too few women—to be informative. And families are getting smaller because of

few births as well. Hence, the topic—as important as it is controversial—is timely. We expect that this meeting will be highly influential and will receive extensive notice internationally.

For all the scientists and physicians whose work is being supported by the CBCF we extend our gratitude and appreciation. Innovation requires intellectual freedom, which is what your philanthropic support assures. We are confident that the scientific advances made possible by the CBCF will help thousands of people and lead toward the control and ultimate eradication of breast cancer and related diseases. We remain dedicated to this mission and energized by the confidence you express by your steadfast generosity.

Sincerely,

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