Memorial Sloan-Kettering Cancer Center

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Dear Andy,

As we end another year of generous funding from the Cure Breast Cancer Foundation I would like to take this opportunity to thank you and the organization for allowing us to move forward on a number of projects that are linked by our expanding knowledge of the mobility of breast cancer cells.

As is well known to your group, cancer is as much a disease of cell movement as of cell division. Indeed, the spread of cancer cells beyond the immediate vicinity of the breast (called "metastasis") is the major cause of mortality from breast cancer. However, heretofore we have neither understood this process in depth nor have we developed specific therapies to interfere with it. Yet a major advance has been accomplished in the laboratory of my close colleague Joan Massague in which it has been proven that cancer cells can circulate in the blood and come back to the tumor of origin. This self-seeding invigorates tumor growth by a variety of mechanisms, which are under intense study. Hence our understanding of cancer seeding is improving quickly, with its clinical aspects being explored in no small measure due to the support of the CBCF. Indeed, your grant has provided an essential umbrella to partially support and primarily unite diverse activities under my leadership.

Cancer seeds can hide in bone for years to decades before they wake up to grow as bone metastases and/or spread to other organs. This is most common with breast cancer cells that have estrogen receptors and hence require estrogen (from the ovaries or the tissues themselves) to grow. However, it is not the estrogen link that gives them this ability but rather the activity of a gene called SRC, found to be active in 90% of estrogen receptor positive cancers. With CBCF support we are to harvest circulating cancer cells from the blood of women

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without known metastases who are many years after their primary surgical/radiotherapeutic treatment for breast cancer. We will seek to examine these cells for evidence of SRC activation in preparation for a trial of medicinal SRC inhibition in an attempt to clear the blood of these cells as a sign of eradicating them from their bone hiding place.

For the reasons cited in the above paragraph we suspect that bone metabolism may play an important role in the behavior of breast cancers and maybe even in its causation. Bones are constantly being dissolved and re-built as a normal process in humans. Hence, in collaboration with Columbia University we are performing blood tests to measure the activity of the bone formation and destruction (called "turn over") in women with and without breast cancer. We are also conducting a study at the Soroka Hospital in southern Israel that will monitor the bone health of a large, genetically diverse group of women, with a specific focus on the relationships between bone and breast cancer. This study has brought together cancer doctors, endocrinologists, radiologists, and pathologists, providing a specialized, unique team to focus on this and related issues.

Cancer seeds need certain specialized white blood cells to grow. In fact, cancer cells by themselves are quite benign: They need their white blood cells "mates" to form tumors. We are studying this relationship so as to design ways of interfering with it, either killing the cancer cells outright or making them more susceptible to other cancer-killing drugs, like chemotherapy. Furthermore, some special white blood cells seem to be able to inhibit cancer seeds growing in the lung. We have found such cells in the blood of women with breast cancer but not in women without breast cancer. This project will examine many more volunteers in this regard and also start to develop ways to make these cancer killers more plentiful as a treatment strategy.

To study clinical specimens as regards self-seeding we are working with the Cold Spring Harbor Laboratory in the development of ways to analyze the DNA of individual cells. By examining the variations in the DNA in cancer cells we will be able to tell where they come from: hence, we will have the tools to document that cells in the primary breast tumor may have arisen from a metastasis. Furthermore, this approach will help us identify the genes in the cancer cell that drive such behavior, which will help us devise new treatment strategies.

In addition, as mentioned in previous reports, we are exploring several ways of converting cancerous tumors into "poisoned sponges" that can attract seeds but stop them from growing or traveling further. One such approach uses a drug recently approved for the treatment of malignant melanoma, a deadly skin disease whose lethality can be ameliorated to some extent by enhancing the body's own immunological defenses against it. We are about to start a clinical trial attempting to extend this work to primary breast cancer in women, freezing the tumor—thereby releasing signals to the immune system—plus using the drug to unleash a profound immunological response to kill seeds attracted to the site, among others that might be scatted throughout the body.
Work continues on using the mathematics of tumor growth based o the self-seeding concept to improve drug scheduling in anti-cancer therapy. Indeed, a clinical trial using a novel schedule of

an oral taxane is now about half completed, and another with a oral "alkylating agent" is planned. We are also starting to analyze the seeding geometry of cancer images on magnetic resonance images to classify cancers as high seeders with a poor prognosis or poor seeders with a better prognosis. This latter work will also give us tools to interpret the effects of anti-seeding drugs as we test them in patients getting chemotherapy before the surgical removal of their tumors.

As is apparent, with the help of the CBCF we have embarked on many studies with great promise of helping us understand seeding in a clinical context and disrupting same with the goal of treating—and ultimately curing and preventing—breast cancer. All of us involved in this mission wish to express our appreciation for this support. Your steadfast encouragement of our work is already bearing fruit. We are delighted to share with you our conviction that the strides enabled by the CBCF are moving us closer to the day when we can proclaim victory over this disease.

Sincerely and with Gratitude,

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