Memorial Sloan-Kettering Cancer Center

Larry Norton, MD
Deputy Physician-in-Chief, for Breast Cancer Programs
Medical Director, Evelyn H. Lauder Breast Center
Norna S. Sarofim Chair of Clinical Oncology

Andrew B. Abramson
Cure Breast Cancer Foundation, Inc.
1122 Clifton Avenue
Clifton, NJ 07013

April 16, 2012

Dear Andy,

It is a pleasure to provide this update regarding the work at the Memorial Sloan-Kettering Cancer Center made possible to a large degree by the generosity of the Cure Breast Cancer Foundation.

As we have presented to the CBCF in the past, the focus of these projects is a new but proven theory of cancer. The theory has evolved from our discovery that cancer cells that break free from the primary tumor mass can circulate in the blood and then reseed that tumor as well as metastatic sites. This observation explains many previous mysteries in cancer medicine, including the mathematical growth pattern of cancer. Our goal is to use an expanded understanding of cancer to design better means of diagnosis, treatment, and prevention, and thereby move us closer to our goal of a complete eradication of breast cancer as a disease.

You have also received separately a report of the project you are supporting at the Soroka Hospital in Israel. This work, which is connecting bone health with breast health, is directly relevant to the self-seeding theory. It is our hypothesis that weak bones could send out chemical signals that promote cancer cell mobility, thereby contributing to carcinogenesis (the inception of cancer) as well as metastatic behavior. I wish to emphasize that the Soroka Hospital is uniquely positioned to conduct this research, by virtue of the large population it serves exclusively; the hereditary, ethnic, and cultural diversity of that population; the excellence of its medical records; and the skill and commitment of its medical and research staffs.

The projects supported by the CBCF at MSKCC involve several principal investigators in addition to myself: Drs. Elizabeth Comen, Heather McArthur, and

Evelyn H. Lauder Breast Center
300 East 66th Street | New York, NY 10065
Phone: 646-888-5319 | Fax: 646-888-4924
nortonL@mskcc.org | www.mskcc.org

Monica Fornier, medical oncologists specializing in breast cancer; Dr. Monica Morrow, specialist breast surgeon; Drs. Edi Brogi, Hanna Wen, Dilip Giri, and Marcia Edelweiss, specialist breast pathologists; Drs. Simon Powell and Alice Ho, specialist breast radiotherapists; Drs. Robert Benezra, Johanna Joyce, and Gaorav Gupta, cancer biologists; Dr. Ross Levine, hematologist and cancer biologist; and Dr. Martin Fleisher, clinical pathologist. Dozens of co-investigators are also involved.

MSKCC has other activities related to self-seeding, especially those in the independently funded laboratory of Dr. Joan Massague, the co-originator of the concept. The infrastructure provided by CBCF funding allows for the integration of those activities with the ones specifically supported by CBCF, as described below.

Self-seeding attracts cancer cells to the primary site. Were we able to augment the ability of the primary tumor to draw in cancer cells (the "sponge" effect) and then kill them (a "poisoned sponge"), the benefits to the patient could be considerable. Accordingly, we have embarked on a clinical trial combining cryoablation (freezing) of a primary breast cancer—which releases chemicals that attract cancer cells and stimulates immune white blood cells—with a drug that releases a chemical break so that the white cells so attracted can attack and destroy the cancer cells. Thereafter, when the tumor is removed as part of standard therapy, we will examine it as well as the peripheral blood of the patient for evidence of immune stimulation. Upon successful completion of this pilot study we will consider a therapeutic trial of this cryoablation/immunotherapy program in conjunction with standard therapy *vs.* standard therapy alone to assess the actual benefits associated with this new plan of anticancer treatment. For future projects we are also considering using radiation therapy instead of or in addition to cryoablation.

Cancer cells that seed the bone may rest there for decades in a so-called latent or dormant state before awakening to form bone metastases and/or seed other organs. There is evidence that the Src gene is implicated in this process. In addition, a molecule called RANK-ligand may be very important for allowing the cancer cells to destroy bone. Accordingly, we are studying these factors in bone metastases. We are also planning to collect circulating cancer cells from the blood of people with bone metastases and those at risk of developing bone metastases to study these and related molecules. Part of this work involves the ability to describe the entire DNA molecule (called "sequencing") in individual cells. We are collaborating with colleagues in the Cold Spring Harbor Laboratory in developing better and less expensive methods for accomplishing this goal. In addition, we plan to use single-cell-sequencing technology to examine primary cancers for evidence of cells that arose in metastases, thereby providing further proof of self-seeding in breast cancer patients.

We are conducting a number of studies of "triple negative" breast cancer (TNBC). This type—characterized by the absence of receptors for estrogen and progesterone as well as normal levels of HER2—is the most active self-seeder and distant-seeder. We are looking for specific mutations in these cancers that may explain their

behaviors, in particular their patterns of metastases, including metastases to the axillary (arm pit) lymph nodes. TNMB is the type that most commonly occurs in women carrying inherited mutations in BRCA-1. Accordingly, we are studying the BAP-1 gene (BRCA-1 Associated Protein) in these cases, attempting to understand the cause of self-seeding on a molecular level. We are planning to ascertain if mutations and other chemical characteristics in TNBCs affect their sensitivity to radiation therapy.

A cancer cell by itself is harmless unless it can gather around white blood cells that support its growth and other white blood cells that can turn into blood vessels. Once these white blood cells are recruited, the cancer cells join with them to form a tumor mass, which is the means by which a cancer destroys the function of vital organs. Hence, in addition to studying cancer cells we are also examining the white blood cells that infiltrate the tumor mass. One set of studies involves molecules called cathepsins that are critical for the relationship between the cells and the normal cells of the breast. Most recently we have considered the possibility that the white cells that infiltrate the cancerous mass are not normal, but harbor mutations, including mutations similar to those found in some leukemias. Were this confirmed, we could develop drugs that attack those white blood cells, robbing the cancer cells of sustenance critical for their survival.

Needless to say, the support of CBCF has been essential for the conduct of these projects. For all of the investigators involved and for MSKCC, I express my appreciation to the CBCF for its generosity, enthusiasm, dedication, and commitment. We are making significant strides toward understanding cancer in an entirely new light. As a consequence, we have every reason to believe that our discoveries will translate into cancers prevented, lives saved, and progress toward our ultimate goal: a world without breast cancer.

Sincerely,

Larry Norton, M.D.
Professor of Medicine
Weill Medical College of Cornell University