



Memorial Sloan-Kettering
Cancer Center

June 6, 2014

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

Dear Andy and Colleagues:

The generous support of the Cure Breast Cancer Foundation this year has allowed us to make further progress in our mission to decipher breast cancer biology so as to produce clinically relevant results. As you are aware, a major focus of our work is the relationship between mobile breast cancer cells and the “normal” cells in their immediate environment. This is of major importance because it is the mobility of breast cancer cells that allows them to form metastases, the major life-threatening aspect of cancer. Metastases depend not only on the mobility of cancer cells but also their ability to interact with white blood cells, blood vessel cells, and other cells in the organ that they invade. The CBCF has facilitated creative studies of this process leading us toward the development of novel approaches to cancer prognostication, therapy, and ultimately prevention.

Much of our current work derives from the observation that cancer cells can travel throughout the body and invade not only other organs but existing tumor masses, including the cancer at the primary site: the breast. Hence, growth of the primary cancer and distant metastasis are fundamentally interrelated. This is why radiation therapy is so crucial after lumpectomy: cancer cells can travel in the blood stream and come back to the normal breast tissue even when the whole cancer seems to be removed by the surgeon. With the support of the CBCF we are exploring the biology underlying these phenomena and are making major discoveries.

As an example, we are working on the relationships between the traveling cancer cells—which are the “seeds” from which metastases grow—and other cells that form cancerous masses, called *tumors*. These other non-cancer cells—white blood cells and blood vessel cells in particular—do not behave normally in the presence of cancer cells. In collaboration with Dr. Robert Benezra and colleagues we were the first to identify a subset of neutrophils that can be “trained” by a primary breast tumor to inhibit cancer spread to vital organs. We were the first to demonstrate a critical difference in neutrophils taken from breast cancer patients compared with those taken from healthy volunteers. We demonstrated that neutrophils isolated from the blood of newly diagnosed breast cancer patients were able to kill breast cancer cells in the laboratory whereas

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those from healthy volunteers were not. Just this past year, we made significant progress in identifying the unique molecules in the blood that stimulate neutrophils in breast cancer patients. We are now using this knowledge to develop techniques for stimulating a woman's own neutrophils to function as an effective immunologic barrier to metastasis.

We also discovered that other white blood cells have the opposite effect in that they stimulate tumor growth. In collaboration with the hematologist Dr. Ross Levine and many colleagues we are studying the DNA of these white blood cells. Dr. Levine previously discovered novel genetic mutations associated with leukocytes in certain leukemias. Now, we are the first group to investigate whether mutations can play a role in the interplay between breast cancer and the immune system. This work is progressing very well and we hope to prepare a major report in this regard this year.

One of the most dangerous characteristics of cancer is that the DNA in the cells gets more and more aberrant over time, making the cells progressively more dangerous. It has been thought that each metastasis represents its own isolated step in this process. However, based on evidence that seeding between metastases is an important component as well, we have started a multinational study to examine the phenomenon. This could be of critical importance in that with improved understanding we might be able to develop drugs that inhibit seeding between metastases, clinically limiting the emergence of drug resistance.

In collaboration with bio-mathematicians and the physicists Drs. Peter Kuhn and Paul Newton we have developed a mathematical model of breast cancer metastasis. Using data from over 400 patients, we developed a predictive model of breast cancer growth which will help doctors and scientists where breast cancer may spread next in a patient. This work provides a novel organ specific model of breast cancer metastasis and in turn uniquely informs research into metastasis prevention.

In another set of experiments our colleagues in Israel and New York are evaluating the relationships between bone health and breast cancer. Bone is the main organ that can harbor cancer seed cells in a dormant state, feeding later metastases to the bones and other organs. As noted in their report we have confirmed in a retrospective study that increased bone density seems to be related to breast cancer incidence. That bones and breast are connected biologically is strongly suggested by our evidence that at a given bone density women with breast cancer develop fractures more easily even when their bones are not harboring obvious metastases. We are now well into a prospective trial in this regard, which will help us define the phenomenon more exactly, with the eventual goal of intervening so as to reduce breast cancer incidence and metastatic (seeding) potential. This was a major topic in an international symposium that the CBCF supported this year at Soroka Hospital in Beersheba, Israel. The symposium received substantial press attention in Israel and in the United States.

These and other exciting investigations are establishing novel concepts of breast cancer that are, in fact, redefining the disease from one of cell division abnormalities to one in which abnormal cell mobility is the most prominent feature. Diagnostic and therapeutic progress follows such discover science. The freedom to explore such innovative ideas depends upon unfettered funding from organizations with the vision and dedication so well demonstrated by the CBCF. We join

all the scientists and physicians whose resolve to defeat breast cancer and all types of cancer you so generously support in offering our gratitude and in confirming our continued commitment to this mission.

Sincerely,

A handwritten signature in black ink, appearing to read "Larry Norton".

Larry Norton, M.D.
Deputy Physician-in-Chief, for Breast Cancer Programs
Medical Director, Evelyn H. Lauder Breast Cancer
Norna S. Sarofim Chair of Clinical Oncology
Professor of Medicine Weill Medical College of Cornell University

A handwritten signature in black ink, appearing to read "Elizabeth Comen".

Elizabeth Comen, M.D.
Assistant Attending, Breast Cancer Medicine Service