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

June 7, 2013

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

Dear Andy and Colleagues:

Over this past year the generous support of the Cure Breast Cancer Foundation has contributed to considerable progress in our understanding of breast cancer biology. The theme that has guided the Foundation from its inception is the *self-seeding theory*: a novel but experimentally verified and powerful concept with considerable clinical relevance. The CBCF has facilitated imaginative studies leading us toward dramatically new approaches to cancer prognostication and therapy.

While much of cancer research has focused on the division of cancer cells, self-seeding recognizes that cell mobility is an equally important characteristic of these diseases, and one that might be especially amenable to therapeutic intervention. Cancers kill when their cells travel from their primary site to vital organs and infiltrate then, forming masses that disrupt the function of these organs. This is called *metastasis*. What we discovered is that cancer cells can travel throughout the body and come back to the primary site, reinvigorating it and promoting both growth and the generation of new metastases. Hence, growth and metastasis are fundamentally interrelated.

Most recently, our work at Memorial Sloan Kettering Cancer Center has focused on the relationships between traveling cancer cells—seeds—and "normal" cells that join with the cancer cells to form masses, called *tumors*. The word *normal* is in quotes because the non-cancer cells—white blood cells and blood vessel cells in particular—do not behave normally in such cases, and we suspect might not be normal at all. As you read in the reports of our investigators, we found that some special white blood cells, *entrained neutrophils*, can inhibit metastasis. We are figuring out how they do so and are developing methods to stimulate this phenomenon as a means of cancer therapy. Other white blood cells have the opposite effect in

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

NCI-designated Comprehensive Cancer Center

that they stimulate tumor growth. We are examining the DNA of these cells, seeking the changes—mutations—that allow them to behave so, with the goal of learning how we can kill such cells or otherwise inhibit their cancer-stimulating actions.

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 prone to traveling and being destructive. This is called *genetic lability*. It has been thought that each metastasis represents a step in this process. However, very recent evidence suggests that seeding between metastases is an important component as well. The immediate relevance is that if a cancer cell in one metastasis mutates toward resistance to treatment it might seed other metastases throughout the body, leading to poor treatment outcomes. As noted in our reports we are embarking on a multinational study to examine this, which could be one of the most important studies in modern cancer biology. This is because if we confirm the phenomenon and understand it better we might be able to develop drugs that inhibit seeding between metastases, limiting the emergence of drug resistance in practice.

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 conducting 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.

These and other promising investigations are redefining breast cancer, leading us in innovative and exciting new directions. I emphasize, as I have in years past, that the freedom to explore fresh ideas depends upon unfettered funding from organizations with the vision and passion so well exemplified by the CBCF. On behalf of the scientists and physicians you support, whose dedication to eradicating breast (and all) cancers is sustained by your generosity, I offer our gratitude and continued commitment to our shared goals.

Sincerely,

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