Memorial Sloan Kettering
Cancer Center

March 21, 2023

Mr. Andrew Abramson
Treasurer/Co-Founder
Cure Breast Cancer Foundation, Inc.
1122 Clifton Avenue
Clifton, NJ 07013

Dear Mr. Abramson,

This year has been an extraordinary year of productivity for the CBCF research program, dissecting the fundamental cellular machinery of cancer with a focus on meaningful clinical applications. Attached are more detailed reports on progress from our two main laboratories: that of Dr Ross Levine (Memorial Sloan Kettering) and of Dr Rachel Hazan (Albert Einstein College of Medicine).

From its inception, the CBCF has sought to transform breast cancer management by revolutionizing our concept of cancer as primarily a disease of cell division to one in which cell mobility—and the relationships between cancer cells and their environment—plays a dominant role. This is leading to a new understanding of prognostic factors (important for making clinical decisions) and the identification of new targets for therapy and, ultimately, cancer prevention.

The Levine laboratory has focused on mutant white blood cells that are now known—because of our work—to infiltrate most breast and other cancers. This is a major shift in the conventional cancer paradigm, which since the discovery of DNA has assumed that the only mutations (abnormalities in DNA) of importance were in the cancer cells themselves. The CBCF, from its inception, has been interested in the discovery that cancer cells do not stay put but move to new locations (say from the breast to the bones or vital organs, called *metastases*) and even go through the blood stream and come back to the primary tumor, with such *self-seeding* unfortunately invigorating tumor growth. We discovered that when this phenomenon occurs, the travelling cancer cells bring white blood cells with them and furthermore, those blood cells often have DNA aberrations too. It is now known that such mutant white blood cells are found in the circulation of otherwise healthy people too, where they predispose to heart disease and convey an increased risk of developing blood cancers. In cancer, the presence of these cells—called clonal hematopoiesis or CH—is associated with a worse prognosis, meaning that they have biological importance.

Larry Norton, MD FASCO, FAACR

Senior Vice President, Office of the President
Medical Director, Evelyn H. Lauder Breast Center
Norna S. Sarofim Chair of Clinical Oncology

EHL Breast and Imaging Center, 300 East 66th Street, New York, NY 10065 T 646.888.5319 F 646.888.4924 www.mskcc.org
NCI-designated Comprehensive Cancer Center

Analyzing clinical data on thousands of patients and in addition, using unique laboratory models that were created by us, we now strongly suspect that the main activity of these CH cells is in impairing the immunological response to the cancer. This seems to apply to hormone sensitive breast cancer, HER2+ breast cancer, and triple-negative breast cancer, which therefore includes all the main types. Moreover, the effects depend upon the specific mutations in the CH cells. As detailed in the attached report, we now have sophisticated molecular and biochemical tools for analyzing these phenomena in great depth. The intention of our work is to develop interventions to disrupt the immune-suppressing effects of these cells so as to increase the activity of immunotherapy against breast (and other cancers). Our expectation is that this will be a significant clinical advance.

The Hazan laboratory is arriving at a basic understanding of the changes in the cancer cell that underly its mobility and hence self-seeding abilities. There are various states of a cell, from fixed (epithelial or the E state, the normal state) to mobile (mesenchymal or the M state) or a mixture (called E/M). This laboratory discovered that the E/M state is the most dangerous regarding the promotion of self-seeding and hence metastatic behavior. Furthermore, we have discovered the molecules responsible for that state shift (FOXC2→TCF1→Wnt/beta-catenin). By using sophisticated analytic methods, as detailed in the report, we are gaining an understanding of the genes underlying this process, which is the first step in developing drugs to block it.

A combination of anti-seeding drugs and novel immunotherapies could be transformative in cancer medicine, enabling us to create strategies that are more effective and less toxic than many current approaches—like chemotherapy—that are non-specific and hence hurt normal cells as well as cancer cells. The conceptual basis for these advances in the self-seeding model, which has long been championed by the CBCF, which has also been the critical source of financial and intellectual support. For the scientists and the public we serve, we thank the CBCF for its unswerving backing and encouragement and look forward to another year of great progress in 2023.

Sincerely,

Larry Norton, MD FASCO, FAACR
Senior Vice President, Office of the President
Medical Director, Evelyn H. Lauder Breast Center
Norna S. Sarofim Chair of Clinical Oncology