Memorial Sloan Kettering
Cancer Center

March 7, 2019

Dear Andy and Friends:

It has been an extraordinary year of achievements in the research that the CBCF's support has made possible. We are confident that with your sustained enthusiasm and generosity we will continue to make meaningful insights into the nature of cancer and advance both scientific and clinical progress. Our goal is not just incremental improvements, but dramatic strides toward total control of breast cancer and all neoplastic diseases.

As you know, our area of focus started with the discovery that cancer is as much a disease of cancer cell mobility as of cancer cell division. That is, cancer cells not only make new cancer cells by cell division (mitosis) but they also have another key property that contributes to the growth of a mass (tumor). That is, they can enter the blood stream and return to their place of origin or go to new sites (such as breast cancer cells traveling to the bones). New sites are called *metastases*. When there are two or more sites of disease the cancer cells can move between sites. We termed this process of mobility *self-seeding*.

When the cells move they bring white blood cells and blood-forming cells with them, invigorating the cancer cells' propensity to divide, making new cells. Most anti-cancer drugs attack cell division because in the past it was thought that cancer was mostly a disease of cell division. But now we know that self-seeding is as much a possible target of therapy as is cell division. This insight has motivated research on developing anti-mobility drugs to combine them with anti-mitotic ones. We now have several leads in this regard, with one new drug (an anti-YAP/TZ/hippo compound) being screened for efficacy in our laboratories.

One of the most provocative observations concerning self-seeding is the involvement of white blood cells (*leukocytes*). We all know that white blood cells are the immune cells that fight infections and sometimes fight cancers. But some white blood cells have another role: stimulating cancer cell growth and mobility. It is a true *yin/yang* situation: anti-growth/pro-growth at the same time. It was for this reason that we started examining the DNA of leukocytes found inside of cancers (called tumor infiltrating leukocytes, or TILs). Cancer cells have been known for decades to have mutant (altered) DNA. We made the remarkable discovery that supposedly normal immune cells infiltrating common breast cancers are often mutant, with DNA changes commonly associated with malignancy. This was never suspected before.

Over this last year we have focused on studies of these mutant leukocytes. What role to they play in stimulating growth? Are these mutant TILs a possible therapeutic target? Do they suppress the ability of cancer-killing leukocytes (activated T-cells) to do their job? When patients develop other diseases—heart disease, other cancers, leukemia—do these mutant TILs play a role?

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This later concept has been given force by a dramatically expanding area of interest at MSK called *clonal hematopoiesis* (CH). It turns out that about a quarter of patients with cancers (not just breast cancer) have leukocytes in their circulating blood that harbor these same cancer-causing mutations. We are studying the relationship between CH and prognosis, response to anti-cancer therapy, the presence of mutant TLs and the occurrence of other diseases after a cancer is cured. We are also studying the relationship between CH and mutations you might inherit from a parent that predispose you to getting cancer. All this work is very likely to transform our concept of the very nature of neoplasia, from strictly a disease of abnormal cell division to one not only of mobility but of relationships between the cancer cells and (previously assumed to be) normal cells in their vicinity. Diagnostic, prognostic, therapeutic and preventative advances could well follow rather quickly from these investigations.

Because of the CBCF this next year will see scientific activity both in the laboratory and clinic that will help answer our critical questions. We are especially excited by ongoing discussions with a network of academic centers that have conducted ground-breaking research on determining which patients with early breast cancer need adjuvant chemotherapy and which have such a good prognosis that chemotherapy is not needed. What role CH and mutant TILs have in this setting could not only illuminate basic mechanisms of cancer but could give us better prognostic and predictive tools as well with which to counsel individual patients.

One other important finding related to self-seeding deserves mention. By studying the growth curves of cancers before and after chemotherapy we have suspected that chemotherapy not only kills cells but does something to blunt that killing at the same time, a sort of feedback mechanism that can prevent total cancer eradication in some cases. With Dr. Rachel Hazan at Albert Einstein College of Medicine we found that chemotherapy stops cancer cells from dividing (i.e. is anti-mitotic) but at the same time can increase self-seeding (i.e. is pro-mobility). The molecular switch responsible is a molecule called *p21*. We now suspect and hope to prove this year that the mobile cells, because they are not dividing, are resistant to the killing effects of chemotherapy. They circle back to the tumor from their protected environment (the blood circulation) and replenish the cancer, partially diminishing the benefits of the chemotherapy. Of course, the answer to this problem would be to combine anti-mitotic and anti-mobility drugs together in cocktails, which gives further impetus to the search for anti-mobility drugs described above. Ways of modulating the p21 response are also possible and is a further area of research.

The CBCF's support for a new center of oncology research in Southern Israel has also born fruit this year in the opening of the Dr. Larry Norton Institute at Soroka Hospital (Israel's second largest) in Be'er Sheva. Superb work on the relationship between bone health and breast cancer is proceeding there and a fascinating abstract about recent findings—that a history of breast cancer weakens bones independent of the degree of bone mineral density measured by a DXA bone scans--has recently been submitted to a major European meeting. The Institute will have a significant impact on global heath because of the unique combination of a large, genetically-diverse population, electronic medical records, near universal health insurance and a talented, dedicated staff of physicians, nurses, and scientists to conduct laboratory and clinical research in a coordinated fashion. A special focus of the Institute is mathematical oncology: The application of the most advanced techniques of image analysis, machine learning, and artifical intelligence to topics such as gene-gene interactions, digital pathology, and tumor growth kinetics.

These projects illustrate that the CBCF is enabling much novel, engrossing, and clinically-relevant research with extraordinary potential to help cure and even prevent breast cancer and thence many other types of cancer. For this the physicians and scientists involved in these projects are deeply grateful. We remain heartened by your dedication and generosity. For us and the current and future patients we all serve, please allow me to express our profound appreciation.

Sincerely,

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