



**Larry Norton, MD**

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Dear Andy and Colleagues;

The support of the CBCF has been essential for the nurturing of an idea that has the potential to change our understanding of and approach to many cancers, especially breast cancers, in fundamental ways. While the idea came from several directions and has been developed in several laboratories, the freedom afforded by the flexible funding from the CBCF has encouraged novel explorations that would not have been possible otherwise. The work has already been well received by the clinical and basic science communities and - again with the help of the CBCF - should expand exponentially over the next few years.

The basic concept, termed *self-seeding* in recent publications, represents a confluence of two fields of quite disparate research, and thus illustrates the synergy always sought by laboratory and clinical scientists. The laboratory side of the project derives from the ground-breaking work in the laboratory of Sloan Kettering Institute's Dr. Joan Massague, one of the most accomplished and celebrated biologists of our time. Dr. Massague and colleagues have been studying the mechanism of metastasis, which is the spread of cancer cells from their tissue of origin, like the breast, to distant organs, like bone, lung, or liver. They have found that the activity of specific gene sets allow cancer cells to spread to specific organs. These genes turn on specific, now defined functions in both the cells themselves and normal cells attracted to the metastatic sites as facilitators. With my help, Dr. Massague hypothesized that the cancer mass itself may be a "metastatic" site, with circulating cells re-seeding the tumor, enriching it with the worst cancer cells. This hypothesis has now been proven to be true in animal models of breast and other cancers, and thus represents an entirely new mechanism for cancer growth and progression over time. Studies aimed at finding evidence of self-seeding in human cancers are currently underway.

I, a biomathematician in addition to being a clinical scientist, have been studying the growth patterns of cancers for many decades. With my colleague Dr. Richard Simon at the National Cancer Institute, I recognized that a well known pattern of growth - first described by Benjamin Gompertz in the early 19th century - could be used to plan more effective and less toxic anti-cancer therapy. This too has been proven to be true in the laboratory and the clinic, and is now the basis for many highly effective cancer treatments for many diseases including breast cancer. The biomathematical side of the self-seeding concept is that this biological mechanism of growth explains the applicability of the Gompertz equation to cancers. In other words, self-seeding is the cause of Gompertzian growth. Indeed, a new equation arose from this work, the *Norton-Massague Model*, that has already been accepted by biomathematicians worldwide as a useful expression of Gompertz' original observation.

With the support of the CBCF much has already been accomplished in the maturation of these ideas. The most concrete example has been the application of the Norton-Massague equation to the prediction of optimal doses and schedules of anticancer drugs. One such drug, an oral taxane, is now in clinical trial using the schedule predicted to be best by this method. Several other drugs are in study and might be in

clinical trials within the next year. One of the most exciting in this regard is one that could make breast cancer cells that have become resistant to hormonal therapy sensitive again. The development of this mathematical approach is a significant advance in that prior to its creation there was no logical way to use laboratory models to pick optimal schedules to be used in initial clinical trials. Many drugs fail in the clinic not because they are not active in hurting cancer cells, but because they are not tested at the right doses and schedules. The Norton-Massague equation provides an approach to help ameliorate this impediment to progress.

At present there is much research underway to better understand the mechanisms and clinical implications of self-seeding. One of these, currently being supported by CBCF, is a study of human cancer cells in mice to see if a particular type of normal white blood cell can prevent seeding, a concept for which we have preliminary evidence. Another CBCF project will see if irradiated tumors can still attract seeds. This project may change our approach to radiation therapy of breast cancers in that we now do radiation to the breast after surgical removal, but perhaps it should be done first! In all of these studies, we are examining how the self-seeding of the modified primary tumor affects the development (especially in inhibition) of metastases elsewhere.

Another major project, also being funded significantly by the CBCF, is examining the relationship between osteoporosis and the development and progression of breast cancer. This work, multinational in scope, builds upon another set of key observations from the laboratory of Dr. Massague. He has found a mechanism by which breast cancer cells can silently reside without dividing (i.e. remain dormant) in bone for decades after the therapy for the disease in the breast. We plan to use CBCF funds to help conduct a study of cancer cells in the blood of patients to see how many of these cells have the genetic markers of bone-seeking cancer cells. Based on this work we plan to eventually study specific drugs that attack the molecular basis for bone-seeking.

Another CBCF supported project will examine the prognostic implications of self-seeding in human breast cancers by analyzing the fractal geometry of specimens and correlating the information so gathered with outcomes.

All of these examples are focused both on improving our understanding of breast and other cancers and the clinical translation of such improved understanding to the better management of these diseases. The CBCF is the major supporter of this mission, indeed a partner in our quest. New ideas will certainly emerge while we pursue the aims stated above, which we will be able to examine because of the freedom that CBCF support provides. Most other funding sources are restrictive and hence do not permit such intellectual liberty. Moreover, the excitement we share with CBCF supporters is a constant source of encouragement and motivation for those of us who fight cancer with science every day. We will make progress, and we will do so together.

Sincerely,

A handwritten signature in black ink, appearing to read 'Larry Norton', with a long horizontal flourish extending to the right.

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