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The Cancer Seed and Soil Hypothesis

One in 2 men and 1 in 3 women in the US will get cancer. Five decades after declaring war on the disease, we are still muddling our way rather blindly from the slash-poison-burn (surgery-chemo-radiation) strategies to newer approaches like targeted therapies, nanotechnology, and immunotherapies which benefit only a handful of patients. Among other reasons for the slow progress, a major flaw is the study of cancer cells in isolation, which de-links the seed from its soil.

Stephen Paget was the first to propose in 1889 that “seeds” (cancer cells) preferentially grew in the hospitable “soil” (microenvironment) of select organs. The cross-talk between seed-soil hypothesized by Paget indeed proved to be the case whenever the question was examined (such as in the elegant studies of Hart and Fiddler in the 1980s). Yet, consistent research combining studies of the seed and soil were not pursued, largely because in the excitement generated by the molecular revolution and discovery of oncogenes, the idea of creating animal models of human cancers appeared far more appealing. This led to the entire field of cancer research being hijacked by investigators studying animal models, xenografts and tissue culture cell lines in patently artificial conditions. The result of this de-contextualized approach, which is akin to looking for car keys under the lamppost because of the light instead of where they were lost a mile away, is nothing short of a tragedy for our cancer patients whose pain and suffering some of us witness and try to alleviate on a daily basis.

Many of my fellow researchers are probably rushing to attack me for making misleading statements and ignoring the great advances they have already accomplished in oncology using the very systems I am criticizing. I should know; I am still receiving hate mail for answering the *Edge* 2014 Question about what idea is ready for retirement by saying that mouse models as surrogates for developing cancer therapeutics need to go. I am sorry to remind them that we have failed to improve the outcome for the vast majority of our cancer patients. The point is that if strategies we have been using are not working, it is time to let them go. Or at least stop pretending that these mutated, contrived systems have anything to do with malignant diseases in humans. Both the funding agencies and leaders of the oncology field need to admit that the paradigms of the last several decades are not working.

The concept I want to promote is that of Paget's seed-and-soil approach to cancer and urge a serious examination of cancer cells as they exist in their natural habitats. Basic researchers want to know what they should replace their synthetic models with. My answer is that first and foremost, they should work directly with the clinical oncologists. If methods to recapitulate human cancers in vitro don't exist, then we must prepare to study them directly in vivo. We have a number of effective drugs but these usually help only subsets of patients. It would be a tremendous step forward if we can match the right drug to the right patient.

For example, in the study of leukemia, we could start by treating patients with a study drug while simultaneously studying freshly obtained pre- and post-therapy blood/bone marrow samples with pan-omics (genomics, proteomics, metabolomics, transcriptomics) technologies. A proportion of patients will respond and a proportion will fail. Compare the pan-omics results of the two groups and then design subsequent studies to enrich for subjects predicted to respond. It is likely that a few more patients will respond in round two. Repeat all the studies in successive clinical trials until identifiable reasons for response and non-response are determined.

If this exercise is undertaken for each drug that has shown efficacy, within the foreseeable future, we will not only have accurate ways of identifying which patients should be treated, we will be able to protect the patients unlikely to respond from receiving non-effective but toxic therapies. Besides, the pan-omics results are likely to identify novel targets for more precise drug development. In this strategy, each successive trial design would be informed by the previous one on the basis of data obtained from cancer cells as they existed in their natural soil.

Readers are probably wondering why such obvious studies based on patient samples are not being done already. Sadly, there is little incentive for basic researchers to change, not only because of the precious nature of human tissue and the difficulties of working with harassed, over-worked clinical oncologists (mice are easier to control) but also because of resources. I am aghast at funding agencies like the NIH who continue to prefer funding grants that use an animal model or a cell line. After all, who makes the decisions at these agencies? As Gugu Mona, the South African writer and poet has noted: "The right vision to a wrong person is like the right seed to wrong soil."