

**3rd Annual Town Hall Meeting**  
**Translating Breast Cancer and Environmental Research into Action**

*Location! Location! Location!*  
*How the Neighborhood Contributes to Breast Development and Cancer*

Zena Werb, PhD  
BABCERC Principal Investigator  
Biology Study  
Professor and Vice-Chair of Anatomy, UCSF  
Member, UCSF Comprehensive Cancer Center

Zena Werb, PhD, began her presentation by emphasizing that it is the environment in which the epithelial cells find themselves that plays a significant role in whether a cell decides to progress to cancer or just remains in a quiescent state. The parallel she drew was the difference in environments that children grow up in and the influences they have upon those children. For example, does the environment determine whether a child grows up to be a drug dealer or a scientist? Similarly, the way in which a cell behaves has a lot to do with the unique environment in which it develops.

We have millions and millions of cells in our bodies that undergo mutations throughout the course of everyday life. Why do all of these millions of cells **not** become cancer? Why will only one in three or four of us actually get cancer even though each one of us has millions of cells that have received mutations? The changing ecology or the environment those cells find themselves in may be the thing that pushes a cell in one direction or another.

Dr. Werb presented this hypothesis: during normal mammary gland development, cells are dividing, invading the mammary fat pad and moving around, but they do us no harm. Cancer cells act similarly, but eventually do cause us harm. What forces are at work? If we can understand what happens during normal breast development, we may begin to understand the changes in those same events that lead to the creation of cancer environment.

Dr. Werb focuses her research on pubertal development, mostly in mice. During early pubertal development, only the nipple and the beginning of early mammary ducts or tubes are apparent. A few weeks later, there is a fine network of ducts that fill the entire mammary fat pad. At the end of each of these ducts, there is a sub-organ that is pushing and dividing to fill up the fat pad. The ducts are bilayered. You have cells that are tightly attached to each other forming the inside of the tube where eventually milk will be produced, and they are surrounded by other cells, myoepithelial cells, muscle cells, which are going to squeeze the milk out during lactation. At the ends of these stable ducts where the growing and pushing is occurring, you see a much different configuration. There are multiple cell layers in a different organization without a duct. This is where most of the cell division is occurring. Why, in one case, is it part of the

normal developmental process, and in another case, it may be the beginning of abnormal cell growth?

This leads directly to the hypothesis that maybe it is the neighborhood—the other cellular structures in the ducts—that contribute to whether a duct develops normally or develops cancer.

All neighborhoods are composed of many different things, including the extracellular matrix, which creates a structure or scaffolding that holds everything together. Fibroblasts make up some of that scaffolding material, as well as being important in wound healing. Macrophages eat bacteria and also produce factors that make these cells grow. There are many other kinds of cells present in addition to the blood supply that feeds the system. This is referred to as the microenvironment. It has been found that if some of these cells are missing, the organ in question will develop more slowly or poorly.

During puberty, and to some degree during menstrual cycles, a normal duct changes from its resting state to become multilayered. It begins to divide and proliferate. The microenvironment allows that to happen and it also allows the duct to go back to its resting state. The changes are reversible.

One of the questions Dr. Werb and other scientists hope to answer is: what is it in the microenvironment that allows the normal developing duct to stop proliferating and revert back to a resting state? What is different in the microenvironment of the cancerous duct that prevents its return to a resting state?

High-density breast tissue is considered to be a risk factor for breast cancer in post-menopausal women. Some of that risk is due to the scaffolding that holds the mammary ducts together. Researchers are asking whether this scaffolding helps cancer cells move. When normal and cancerous ducts are placed in the abnormal environment of a dense breast, each type of duct subsequently acts abnormally. This outcome suggests that the abnormal environment causes normal cells to behave abnormally, though researchers have not yet discovered the answer as to why this happens.

This question returned us to Dr. Werb's initial premise, which asked how the microenvironment might be altering cell behavior and how that contributes to breast and breast cancer development.