Q&A with Dr. Robert Weinberg

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Cancer biologist and founding faculty member of Whitehead Institute, Dr. Robert Weinberg, discusses breast cancer statistics, his lab's current focus on cancer metastasis, and the long-term effects of declining federal funds for biomedical research.

A Look at Breast Cancer

Q: Can you put breast cancer rates in perspective? Mortality rates in the US have been dropping since 2000, but it's still the 2nd most common form of cancer in women.

According to the most recent statistics, breast cancer incidence rates have been relatively constant in recent years, while mortality rates have been falling for the past 15 years. But we commonly confuse incidence with mortality. Incidence is how often the disease is diagnosed, whereas mortality indicates the rate of deaths. Mortality is a real number; incidence is a cultural artifact, which depends on how often we look for the disease. The ratio with breast cancer is about six diagnosed cases (incidence) to one death (by comparison, the ratio in prostate cancer is five to one), which means that, in the case of breast cancer, six times as many women are diagnosed than die from the disease. You might think the difference between the six and the one is that the other five are cured by the oncologists. However, if you look at the statistics, many women are diagnosed with a form of the disease that isn't lethal and would never become life threatening. These days, the majority of breast cancer survivors are women who have survived a form of the disease that was not likely to ever become deadly.

Do improved diagnostics play a role in this?

From about 1940 to 1990, breast cancer mortality rates went virtually unchanged. However, over the last 20 years the mortality rate has decreased by about 20-25%. This is a real decline, not a cultural artifact, meaning that fewer women per hundred thousand are dying from breast cancer. (This decline is a real tribute to the clinicians who treat the disease—the surgeons, medical oncologists and radiologists.) Indeed, we need to keep in mind that techniques for diagnosing breast cancer have become so sensitive and sophisticated that forms of the diseases are currently diagnosed that wouldn't previously have been detected. The numbers show clearly that most of these were not going to develop into lethal breast cancers. It's common belief that every tumor, if not treated aggressively, will eventually develop into a life-threatening cancer, but the numbers simply don't support this.

Can you provide an example?

By way of illustration, there was a time when the incidence of prostate cancer in the United States was about six times higher than in Denmark, while the mortality rates were almost the same. Why? If you look you will find. If you don't look, you won't find. The same thing is happening with the so-called melanoma epidemic—the curve showing mortality rates from melanoma is flat, but the number of cases diagnosed is increasing steadily.

If a breast cancer is likely non-lethal, how do you determine whether to treat?

Determining whether a breast cancer truly requires aggressive intervention or should be left alone and subjected to "watchful waiting," is an important decision to make. After all, aggressive intervention isn't totally harmless. Chemotherapy and radiation therapy is harmful (one can even develop "chemo brain"). Surgery may also have associated morbidity, and may lead to the outgrowth of new tumors, as post-surgical healing may stimulate the outgrowth of latent tumors. Therefore, since such procedures are not penalty-free, it's important to understand which cancers should actually be treated and those that, at least for the moment, should be left alone.

What advances are being made in determining whether a form of breast cancer is aggressive? What are the challenges with such predictive technology?

The decision about whether to treat a breast cancer either aggressively, or with minimal intervention, should not be taken lightly and is not so easily made. In one case, scientists in the Netherlands use an algorithm that analyzes the genes expressed in a breast cancer, so that a particular cancer can be placed into one of two categories. The top 50% of women have a plausible likelihood of developing aggressive disease and are therefore treated aggressively. The bottom 50% have such a small chance of developing an aggressive form of the disease that the health risks coming from aggressive treatment actually exceed the risk that they will develop metastatic breast cancer. Such technology is helpful, as it's beginning to be employed, but it's still difficult to predict with total certainty which tumors will spread—become metastasized—or which will stay localized. There's always an element of uncertainty in statistical analyses. We are getting better at it, but we could still be years away from the day when we can analyze a tumor and predict its future course with total certainty. Thus, the currently practiced gene analysis can certainly help us understand which genes are being transcribed and expressed, but we still have trouble sorting through this complex data to predict with precision whether or not a patient's tumor is going to become aggressive or not.

Stop Metastasis, Stop Cancer

What is the main focus of your laboratory?

My lab concentrates on metastasis, the process by which cancer spreads from where it first arose to distant locations in the body. Localized (primary) breast cancers are rarely the cause of death. In the case of breast cancer, virtually all mortality comes from metastatic spread. More generally, nine out of 10 of cancer-associated deaths from all types of cancer, come from metastases, not primary tumors. This statistic, on its own, is a compelling reason to focus one's investigation entirely on metastasis—the complex process that allows individual cancer cells in primary tumors to escape and serve as founders of new tumors arising in distant sites in the body. We are interested in understanding how and why metastasis occurs. If you don't understand mechanistically what causes a disease process like metastasis, it's very difficult to develop new ways of treating it therapeutically.

What are you discovering about the metastatic process?

In trying to understand how and why metastasis occurs, we discovered that a biological program, termed the epithelial-mesenchymal transition (EMT), allows cancer cells in a primary tumor to switch from behaving in a benign way to becoming aggressive. By switching on an EMT, a primary breast cancer cell can acquire the ability to seed new tumors by becoming like stem cells—as such, they are called cancer stem cells (CSCs). A CSC also gains the ability to invade and disseminate to distant tissues, a process necessary to create metastatic disease.

How is the EMT program controlled?

We have found a number of signals that activate the malignant EMT program as well as ways of shutting it down. We are very interested in why metastasis formation is actually highly inefficient. For example, it seems that when most migrating cancer stem cells arrive at a distant tissue,they inadvertently shut down their EMT program, losing their "stemness" and thereby foregoing the opportunity to found a metastatic colony.

What other questions are you asking in your lab?

We also want to know how a migrating breast cancer cell, for example, after arriving in a distant site in the body, learns live to in a foreign tissue environment, such as the brain, lungs, or liver. Initially, it's poorly adapted to survive and thrive there. Once in these foreign territories, these cells develop extensive adaptive changes. The nature of these changes is complex and difficult to tease apart at present.

Are these metastatic mechanisms common to all cancers?

Our work involves a class of human cancer known as carcinomas, which represent about 80% of all cancers. The others classes include sarcomas, melanomas, lymphomas, and leukemias, but we work with the faith that much of what we learned is applicable to most cancers.

How far away are you from decoding the metastatic process? And, once you know the processes by which cancer spreads, could you theoretically target them therapeutically?

It's difficult to know how long it will take to decode the metastatic process in detail. And even knowing the exact mechanisms doesn't guarantee that we will be able to target them therapeutically. In our own research, the notion of being able to shutoff the EMT program with a therapeutic agent is an exciting prospect, and we have begun to learn important things in this regard, but we can't focus our efforts exclusively on therapies. Uncovering the basic causative mechanisms of disease processes like metastasis continue to represent the key driver of the development of novel treatments, as it has for many decades. Such "curiosity-driven research" remains the key to such understanding. And if we worried about whether all of our basic research efforts would eventually yield therapeutically useful results, we'd still be in the Stone Age, ill-equipped to develop truly innovative ways of attacking disease.

The State of Funding for Basic Research

What are your thoughts on the state of funding for basic research?

Because of the various financial and economic problems in this country, the future of basic biomedical research doesn't look particular promising at the moment. I never used to think about money. Now I think about it all the time. Indeed, I am continually scrounging around for money—sometimes I'm lucky, often I'm not. It's an ongoing reality that I don't like to communicate to people in my lab for fear they will start thinking about it as well.

What suffers when money for basic research dries up?

I don't look for money for myself, I'm thinking about young people who aspire to careers in research. In the case of cancer research, the rate-limiting step in progress is our ongoing ability to attract highly intelligent, ambitious, and creative young people to work on this problem. But such recruitment takes money for postdoctoral fellowships, RO1-type grants, and junior academic level faculty positions. At this point, in my own case, I can't even think about recruiting attractive post-doctoral candidates because of the uncertainties of current and future funding. Cancer is a complex problem to solve; if throngs of less-than-competent scientists are working on it, we may have the illusion of much effort and success, but actual progress will be slow. The federal government has consciously decided to disinvest in basic research. As a consequence, careers in basic research have become less attractive to young people. The long-term effects of this will be catastrophic, and will only show up 10-20 years from now. We will have lost the best and the brightest who otherwise would have advanced this research. Basic research just isn't attractive right now, and the young people are fleeing in droves.

What will turn the tables? The government? Entrepreneurs? Corporations?

Basic biomedical research creates a pipeline of ideas, and these ideas stoke the fires of therapeutic innovation, but the money for basic research is progressively drying up. I think it's foolish to think that private funding will step in and fill the shortfall created by the missing public funds, because private funding isn't as interested in basic research. Private money wants results, indeed quick results. Philanthropists often want improvements in patient care. Drug companies want something translational. And I don't think that private foundations will have the foresight and the means to support biomedical research the way the United States government has for the past 40 years.

The Future of Cancer

Does lifestyle play a role in breast cancer incidence?

Breast cancer rates vary by more than a factor of ten from one part of the globe to the other, and those differences are not due to genetic differences but rather to lifestyle, largely diet and reproductive practices. This

means that breast cancer development isn't inevitable, despite one's genetic makeup. There are a small number of genetic predispositions, but largely it's a convergence of a number of exterior or lifestyle factors, such as obesity, delayed childbearing, having a small number of children, delayed menopause, and quite possibly certain aspects of diet. As with other types of cancer, the lesson here is a simple one: The best way of reducing the cancer mortality is to avoid developing the disease in the first place.

When might we have a cure for cancer?

As I said, mortality rates from breast cancer are down 20-25% in Western countries, which is a testament to the efficacy of modern treatments. Much of this reduction is due to the cessation of hormone replacement therapy, use of Tamoxifen, Herceptin, radiation of primary tumors, and surgery. Mortality rates will continue to come down over time, but I believe that further progress in this war on cancer will come via a series of successful skirmishes, rather than a one-day victorious battle that yields a cure for all types of cancers.

Written by Dustin Grinnell

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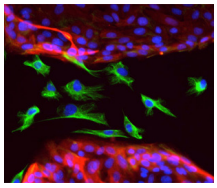

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