Scientists

Scientific Predictions

Robert Clarke

Dean for Research, Interim Director, Biomedical Graduate Research Organization, Professor, Department of Oncology, Lombardi Comprehensive Cancer Center, Georgetown University, Washington DC

Robert Clarke's research into endocrine resistance in breast cancer caught our attention. Curious to know more, *BioTechniques* contacted him to find out about the ambitions, character, and motivations that led to his success.

What has been your most influential scientific contribution?

My colleague Nils Brunner (Royal Veterinary and Agriculture University, Copenhagen, Denmark) and I made a series of endocrine therapy resistant breast cancer cell lines in the 1980s that have served as essential reagents in understanding endocrine resistance at a cellular and molecular level. These cell lines have aided in discoveries made not only by our group, but also by other groups with whom we have shared the cells. I think that developing this tool was probably much more valuable than any individual scientific observation since its influence reaches beyond our own group.

How are you currently using these cells?

In population studies, endocrine therapies lead to a statistically significant improvement in overall survival for breast cancer patients whose tumors express the estrogen receptor. But with advanced estrogen receptor-positive disease, the survival benefit is minimal; we still don't cure many estrogen receptor-positive metastatic breast cancers despite the fact that we have drugs that should work. So, clearly there is something we don't understand and we would like to know what it is.

The cell lines we made model the acquisition of endocrine resistance. The development of this resistance is not controlled by a single gene or pathway. The estrogen receptor sits at the top of a pyramid of signaling events and helps the cell determine whether it will live or die. If the cell chooses to live, will it then proliferate (which is not good if it's a cancer cell) or not? To make these decisions, multiple functions within the cell have to be coordinated. That's why perturbing the estrogen receptor causes such complex, highly integrated, and interdependent effects.

So this really presents a systems biology question: can we understand the system and its functions well enough to make rational decisions about what we want to perturb in order to stop the cells from surviving and proliferating? We're currently working on developing the genomic and bioinformatic tools to generate and analyze these data. Ultimately, we plan to make mathematical and computational models of cell signaling in the context of endocrine resistance in breast cancer. Accomplishing this goal is a large collaborative process. We work with biostatisticians, computer scientists, and engineers because we don't understand all of the principles of the computational biology and they don't fully understand the biology of the system. To be successful, we have to know enough about what each group is doing to be sure that every piece of the puzzle fits.

What is your lab's role in this collaboration?

On a day-to-day basis in my lab, we design experiments and generate the data to which the tools will be applied. Our most important goal is trying to understand how signaling coordinates cellular decisions and where redundancies lie in the system. It's redundancy that gives the cells plasticity and makes them so difficult to kill since they have multiple ways of accomplishing each task. It also makes the system challenging to understand. We can model a linear pathway and think we understand it, but when we perturb it, we discover that there's another

equally important compensating pathway that we haven't considered. We want to learn what those different components are and how they're connected so we can predict how changing one component in the system will affect others. If we can create those models, we can then block multiple pathways, making it more challenging for the cell to make pro-survival and proliferation decisions. My work is translational; we do studies in cell culture, and also attempt to confirm the findings in breast tumors to determine if those signaling events and expression patterns are associated with clinical outcomes.

What is the prevailing thinking for why endocrine therapy does not work as well as it theoretically should?

There are several aspects to consider here. One is a pharmacogenomic component where a gene mutation can alter metabolism of the drug. There is also heterogeneity in expression of the estrogen receptor itself. Cells don't lose the estrogen receptor when they become resistant. In most cases the molecular target for the drug is still present, but the drug either becomes less effective or stops working altogether. Resistant tumors that responded initially to one endocrine therapy quite often will respond to another endocrine therapy. Even as the cells adapt in an attempt to survive the treatment, dependence on estrogen receptor-associated or -dependent signaling remains.

At the moment, we don't have good ways of predicting if individual tumors will or won't respond to treatment. Ideally, we would like to predict the response to each treatment so clinicians can determine which of the endocrine therapies is best.

Interviewed by Kristie Nybo, Ph.D. Image courtesy of Phil Humnicky.

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