

Tackling Drug Resistance Mechanisms in the Stroma

Michael Ostrowski, Ph.D., spent five years at NCI, working with Edward Skolnick, M.D., formerly Chief of the Laboratory of Tumor Virus Genetics (LTVG), and Gordon Hager, Ph.D., now Chief of CCR's Laboratory of Receptor Biology and Gene Expression. Ostrowski is currently Professor and Chair of the Department of Molecular and Cellular Biochemistry at The Ohio State University Medical Center (OSUMC), in Columbus. He is also Co-Director of OSUMC's Comprehensive Cancer Center Program in Molecular Biology & Cancer Genetics.

Death rates for many cancers have fallen during the last several decades, but in some cases, that trend is starting to level off. The death rate for breast cancer, for instance, fell by roughly 25 percent between 1990 and 2010, reflecting advances in targeted therapies such as tamoxifen for estrogen-receptor positive tumors. However, 30-40 percent of breast cancer patients treated with tamoxifen will become resistant to it, and this amounts to a very large number of people for whom we do not have many other treatment options. So while targeted therapies have led to some important successes, we still also have to address the resistance problem. One approach is to address resistance mechanisms specifically within cancer cells. However, in my laboratory, we take a complementary focus upon

the tumor stroma as well, meaning the noncancerous fibroblasts, endothelial cells, and immune cells in the tumor's microenvironment.

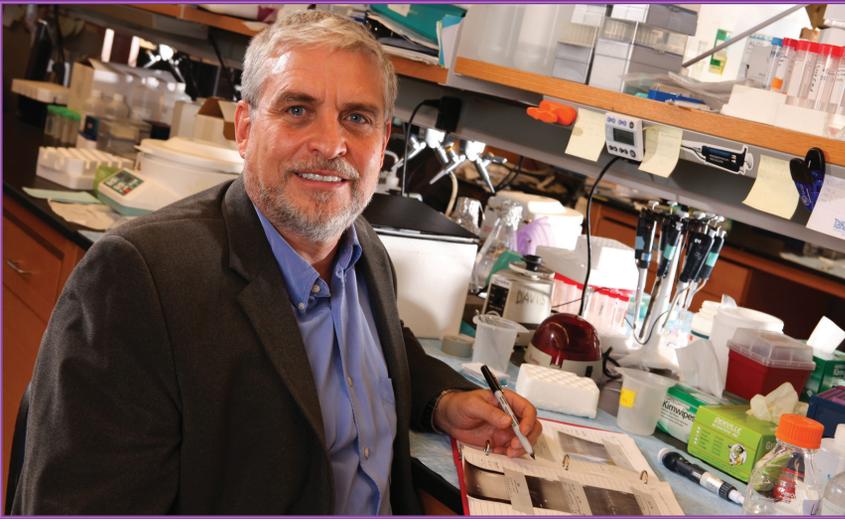
Signaling between stromal cells and tumor cells can drive cancer progression and metastatic spread. My collaborator Gustavo Leone, Ph.D., also from Ohio State University, and I were the first to show that deleting the tumor suppressor PTEN from stromal fibroblasts accelerates angiogenesis and metastasis in a mouse model of breast cancer. PTEN normally suppresses a signaling pathway involving PI3-kinase and a downstream transcription factor known as Ets2, which contributes to cancer progression. Our work showed that deleting PTEN from stromal fibroblasts activates Ets2, and that this makes tumors much more aggressive.

When I came to NCI as a Staff Fellow in 1980, the cloning revolution was just getting under way. In the Hager lab, we cloned the mouse mammary tumor virus and used it to study how glucocorticoids regulate gene expression. These were exciting times to be at NCI as so much was happening in science, and in cancer-related research. NCI was a great training environment, and I had a very productive experience there. Many of the fellows I worked with there have gone on to great careers of their own, and I still collaborate with some of them today. For instance, I collaborate on an NCI-supported Program Project Grant with Morag Park, Ph.D., now at McGill University, who was a postdoctoral fellow working with George Vande Woude, Ph.D.

I also co-direct one of the six scientific programs in our NCI-Designated Comprehensive Cancer Center at OSUMC. What is great about the Center is that it unites faculty from throughout Ohio State, which is a huge university with 16 colleges. We have members from 14 of those colleges,

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(Photo: Courtesy of M. Ostrowski)



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representing a diversity of expertise, from engineering to agriculture to veterinary medicine and even to the humanities, all connected by a focus on cancer.

The Cancer Center also facilitates translational opportunities, and now my laboratory has begun to investigate how stromal PTEN expression correlates with treatment outcomes in human patients. We know that about 30 percent of all human breast cancer patients express PTEN at low levels that trigger Ets2 activation. So we participate in clinical trials that stratify tumors according to PTEN expression, to see if low levels also predict more frequent treatment failures. Targeted treatment with Herceptin (trastuzumab) or lapatinib only works in about half of all HER2-positive breast cancers, and we think that the nonresponders may have deficient PTEN in the stroma. We also know that loss of PTEN and Ets2 activation via PI3 kinase results in the production of secreted factors with an influence on tumor growth: tumors grow faster, become more vascularized,

exhibit more inflammation, and are more resistant to therapy. Our hypothesis is that we can address that deficiency with small molecule inhibitors directed at the PI3-kinase pathway, and that this might break the resistance against Herceptin or lapatinib therapy.

I still see myself as a basic scientist, but with increasing opportunities to move what we do in the laboratory towards the clinic. Our Cancer Center facilitates this translational direction—we identify signaling pathways in humanized mouse models and then we investigate those pathways in human tumors by working back and forth to develop and test hypotheses. Using this approach, we identified more than 200 secreted factors in PTEN-deficient mice, and now we are looking at how the expression of those factors correlates with therapeutic responses in human patients.

We are also starting to work in the area of pancreatic cancer, which is a terrible disease with a huge stromal component. For this cancer, it can be difficult to isolate tumor cells from the stroma, because there is

a high influx of immune cells and a lot of leaky blood vessels. So the translational aspect of our work focuses upon attacking resistance to therapy. And we direct our efforts at the tumor stroma because the cells are genetically stable and, therefore, may be amenable to more durable therapies for which resistance does not pose as much of a challenge.

The stage is set for stromal research to contribute significantly to the survival of cancer patients over the next decade, and I'm excited to be a part of this effort.

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