Fresh Eyes on Metastasis

Jenny Blair writer **Peter Baker** photographer

When cancer kills, it's usually because the tumor has spread, or metastasized. Understanding how metastasis works could offer new ways to get malignancies under control. But the process is fantastically complex—more than any one discipline of science can encompass.

To tackle the problem of metastasis, Andre Levchenko, PhD, the John C. Malone Professor of Biomedical Engineering and Director of the Yale Systems Biology Institute at Yale West Campus, connects researchers working in such different areas that they would not ordinarily even cross paths. Thanks to their resulting conversations, he and his colleagues have made several discoveries that could one day lead to effective blocks on cancer spread.

"We consciously put together a group of people who include physicists, mathematicians, chemists, and people who may not even initially have known a lot about cancer," Dr. Levchenko said. "This very interdisciplinary approach started paying off pretty quickly in new and unconventional approaches."

To leave their tissue of origin and adopt what Dr. Levchenko calls the "more adventurous lifestyle of invading the surrounding tissue," cancer cells have to overcome a series of hurdles. The cells first have to stop multiplying, their inner workings prioritizing "go" over "grow." They must push their way into the circulation, travel, then exit to set up camp in a new place. All the while, they must evade destruction by the immune system and cancer drugs.

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Understanding these changes in behavior requires a careful analysis of the many interacting molecules that trigger them, Dr. Levchenko explained. This understanding should be based on careful modeling of the complex tumor niches to permit both scientific exploration and discovery of interventional targets.

One such discovery required the use of biomedical engineering techniques. His lab developed a surface covered with microscopic ridges that mimics the 3-D environment metastatic cells encounter. When the researchers put cells from brain tumors onto these surfaces, surprisingly they observed that the tumor cells allowed them to accurately predict tumor recurrence in the clinic based on individual cells from actual patients with brain cancer.

Another technique emerging from the interdisciplinary approaches at the institute could greatly speed cancer drug development. Efforts by pharma companies are hampered by the fact that many molecules key to cancer progression are "difficult targets"—proteins whose function and chemical activity are not clear, making it difficult to use the conventional drug development techniques.

In a stroke of insight, a team that includes Farren Isaacs, PhD, and Jesse Rinehart, PhD, at the institute used the techniques of synthetic biology, which can create artificial DNA, to change those proteins in small ways. Those proteins whose tweaks made them biologically active could, in turn, be rapidly tested against thousands of molecules that could inactivate them. A molecule that does so—for instance, one that proves able to block a protein crucial to metastasis—could form the basis of the next breakthrough drug. This led to identification of new drug candidates for brain cancer.

Another way to look at cancer spread involves studying not just the bad actors, but the enablers: Nearby non-cancerous cells and proteins that allow metastasis to take place. That line of thinking informed another of Dr. Levchenko's discoveries, which began with a conversation about the placenta. On walks around Yale West Campus, he and evolutionary biologist Günter Wagner, PhD, the institute's previous acting director, began to talk about the fetal organ that allows for nutrient, waste, and gas exchange. Dr. Levchenko recalled noting several eerie parallels.

"The more Günter was telling me about the placenta, the more I was telling him that it looks very much like cancer," Dr. Levchenko said. "It causes an immune reaction that is suppressed by the mother. It's very invasive, in humans at least. It causes blood vessel growth. If you look at molecules that are involved in placental growth and development," he added, "they're very much the same molecules you find in tumor growth and invasion of tumor cells."

But not all placentas behave this way, as it happens. In humans, the placenta invades the uterus far more than it does in many other animals. What's more, researchers have noticed that animals with less invasive placentas are less likely to experience malignant cancers, and vice versa.

"In horses, where the placenta is not very invasive, melanoma—one of the most invasive and metastatic tumors in humans—turns out to be completely non-metastatic," Dr. Levchenko said.

We still don't know why this is, but Drs. Wagner and Levchenko believe that uterine cells hold a clue. In humans, uterine cells permit placental invasion in much the same way that fibroblasts do. Fibroblasts form the structural framework of our tissues.

To explore this lead, Dr. Levchenko and his colleagues examined differences between cells in cows—which, like horses, are relatively resistant to malignancies—and humans. Those differences, they found, occur not so much in the invasive cancer cells, but in nearby, non-cancerous structural or "stromal" cells. Human stromal cells allow the tumor cells to pass. Bovine stromal cells do not.

Dr. Levchenko compared the situation to an invading army. "Sometimes you have a local population welcoming the army, and sometimes the local population will put up a lot of resistance. In humans, we have stromal cells that are throwing flowers, so to speak, on the invading cells." In cows, by contrast, "they were putting up walls in the way of these invading cells."

The researchers teased out which molecules differed between the species, then they tweaked those molecules in human cells in the laboratory. Those changes made the human cells resistant to tumor invasion.

"We learned how to essentially educate the cells to be more resistant to invasion—and so we immediately had some interesting targets for drug development," Dr. Levchenko explained.

The placenta-metastasis connection "was completely out of the box, an example of how you start thinking about things in an unconventional, orthogonal fashion," Dr. Levchenko said.

These scientific synergies take place not just within the Systems Biology Institute, but also with researchers at the Cancer Biology Institute and Yale Cancer Center. In fact, Dr. Levchenko said, while his lab research into metastasis has been productive, it is important to stay grounded in clinical relevance, "to make sure that what we do is going to be useful."

So he and his colleagues—from engineers to computer scientists to physicists to synthetic and evolutionary biologists—also collaborate with cancer physicians who care for patients with tumors like glioblastoma, pancreatic carcinoma, and melanoma.

"The war on cancer was declared in the 1970s. We've made a lot of progress," he said. "But the war is not won yet. And I think, frequently, progress comes from very unexpected quarters."

Andre Levchenko, PhD