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, then inner workings prioritizing “go” over “grow.” They must push their way through the surrounding tissue, work around blood vessels, and make it to another place. All this requires evading destruction by the immune system and cancer drugs.

Starting with his very first chemotherapy session, Walter documented his progress in photos. Six years later and still in remission, Walter has no lasting side effects other than scar tissue from the radiation and some anxiety. After instituting healthy lifestyle changes, Walter is living a full life and spending time with his 22 grandchildren. He also joined a support group and makes an effort to encourage other patients. The group is now being held virtually, but Walter continues to benefit and share his story with others to give them hope that yes, they can beat this.

Halley Robinson, Licensed Clinical Social Worker for the Thoracic Oncology Program commented, “I have to admit, when we transitioned the group to Zoom, I worried about whether or not the members would continue participating in the same way, but we have thrived in this platform. We are fortunate to have members like Walter, who have faced the uncertainty of a new cancer diagnosis, undergone the stressors and side effects that are commonly associated with treatment, and now, six years out, are thriving. Walter recognizes and validates the difficult days that one might face with lung cancer, while also offering hope.”

“I won’t lie, it was a long, tough road, but the only time I spent in the hospital were those first ten days. I was able to go home after treatment and recovery which was an important to me,” said Walter. “I have 13 children and they took turns, along with my wife Lethie, bringing me in for treatment. I am thankful that I had that support system. I was scared and lost a lot of weight, lost my hair, and was very fatigued. My doctors took excellent care of my physical needs, and my family and faith took care of me mentally and spiritually.”

The five-year overall survival for stage IIIa disease is roughly 23% and the further out Walter gets, the better his odds, explained Dr. Chiang. “He is doing extremely well, and we have every hope and confidence that he will continue to do well.”

Before COVID, Walter and Lethie loved to travel, and plan to do so again once it is safe. “I come from a military family and have lived all over the world including Alaska and England. I enjoy sharing stories of my childhood with my kids and grandchildren,” said Walter. “They were my reason for fighting; they will need me and I was not ready to leave them. People would always say to me, ‘those grandchildren are like medicine to you,’ and they were right. They didn’t fully understand what I was going through, but the love from them kept me going through the darkest times. In a way, they helped save their ‘Papa.’”

Walter is currently on his way to becoming a deacon in his church, New Light Holy Church in New Haven, and at the age of 63 feels that he has a second chance at life. “Dr. Chiang is the best doctor there is. She saved my life, and I’m not sure where I would be without that second opinion, but it doesn’t matter because I am here, thanks to my family and the wonderful team at Smilow.”

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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, 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.”