Danny Welch and KUMC's new Department of Cancer Biology confront the complexities of metastasis

Danny Welch PhD, University of Kansas Medical Center, Department of Cancer Biology

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Danny Welch, PhD, founding director of the University of Kansas Medical Center's new department of cancer biology, wants people to think differently about metastasis. But first, he insists on defining his terms.

"You'd think by now we wouldn't have to worry about defining metastasis, but it's still controversial," Welch says. For starters, it involves more than the ability of some cancer cells to invade new areas of the body.

Before cells that are inclined to spread leave the primary tumor, Welch explains, they begin communicating with stem cells in bone marrow. Those bone marrow stem cells then go to different sites of the body and pave the way for metastatic tumor cells to follow. Most of these tumor cells migrate in clusters — "like teenagers at the mall," Welch says. Others crawl along by shifting their shape, amoeba-like. Still others use a peculiar method called entosis to pass right through other cells. Thinking about this last method, Welch says, "freaks me out because it doesn't make sense — it's like simultaneously breaking through and repairing a brick wall."

When it comes to cancer, even defining a basic word like "migration" is complicated.

Once the cells finish migrating, they need to form cancerous colonies in their new location. Welch considers this "a key component of metastasis" and also the controversial part of its definition, because not all cancer researchers recognize the importance of this final colonization step. He uses the art of Georges Seurat to suggest a different way of looking at things. The late French Impressionist painter developed a technique called pointillism, applying tiny dots of color in patterns to form whole images. Magnifying just one small area of Seurat's *Sailboat* painting, for instance, results in viewers

seeing only pixels; distance is necessary for perspective. "I think we've been so busy focusing on the early stages of metastasis that we forgot to look at the whole picture and give equal attention to this last step," Welch says.

The story of KiSS1

Welch has been hard on the heels of metastasis since 1989. The first gene capable of quashing this deadly process, NM23, had recently been discovered. He was convinced there were others. Several publications from the 1950s — including the first complete chromosome analysis of malignant melanoma cells — had also caught his eye.

Then on faculty at the Pennsylvania State University College of Medicine, Welch observed that as melanoma cells switched from benign to malignant, a particular piece of chromosome 6 vanished about 80 percent of the time. He hypothesized that replacing this missing part would reduce the cells' malignancy — specifically their ability to spread — akin to repairing a runaway vehicle's faulty brakes.

His hunch proved correct. Welch then compared cells with and without chromosome 6, searching for genes that slowed metastasis. He initially called the first one he found SS1 (suppressor sequence 1). "A friend at the NIH told me it was a boring name no one would remember," Welch says. "So I added the letters 'Ki' in front and made it KiSS1, to remind people that it was discovered in Hershey, Pennsylvania. When we went on to find BRMS1 (breast cancer metastasis suppressor 1), we wanted to create a matching set and name it Hug1, but the genome folks said no."

Scientists now know 30 of these metastasis suppressors, six of them discovered by Welch's research group.

KiSS1 normally functions as puberty's master regulator. To figure out how it might muzzle metastasis, Welch's team fluorescently labeled KiSS1-expressing melanoma cells in mice, turning them green and tracking them to the lungs. After nine months, they saw only single melanoma cells in the lungs; when isolated and re-injected under the skin, the cells duly traveled back to the lungs but failed to form tumors there.

"This told us that KiSS1 allows every step of metastasis except growth at the secondary site," Welch says, which proved that KiSS1 is a metastasis suppressor. His group has since shown that beyond melanoma, KiSS1 readily blocks the spread of ovarian, pancreatic and breast cancer cells, at least in the laboratory.

"There are still plenty of unanswered questions," Welch says. "If KiSS1 is given only after metastases have started to grow, will it work? What if we remove KiSS1 after awhile — will those single cells turn mobile and take off immediately, or will there be a carryover effect enabling them to stay dormant? Is KiSS1 working directly on the tumor cells or is an intermediary — think a hired assassin — involved?"

Also, Welch adds, "we still don't know what will or won't happen with KiSS1 as potential therapy. But if we see that it shrinks already-established metastases, even in 10 to 20 percent of patients, I'll be a happy camper."

Metastatic mystery

Researchers are increasingly finding that metastasis, one of the six "hallmarks" originally thought common to all cancer cells, uses a different playbook.

"We now know that not every tumor invades or metastasizes; both are a subset of an individual tumor's properties," Welch says. He suggests that metastasis is better explained by thinking of tumors as seeds that will grow only in the right type of soil — a theory attributed to the late British pathologist Stephen Paget. Welch says that's one reason why metastases "occur preferentially in certain organs, as opposed to wherever the body would take them."

Over the years, researchers have focused on the steps of metastasis deemed most therapeutically promising: invasion, adhesion and angiogenesis, or new blood vessel growth. But these efforts have pretty much failed, Welch notes. For example, clinical trials for anti-invasion drugs — mainly inhibitors against a family of enzymes involved with cell migration — ended in the early 1990s when it became obvious that patients weren't improving.

While metastasis is associated with 90 percent of the morbidity and mortality of cancer, it's still a poorly funded research area. "Fewer than eight percent of researchers mention the word 'metastasis' in their grant applications, in the context of actually working on the problem," Welch says. He'd like this to change. Figuring out how to *prevent* cancer — a key research focus today — would be the best approach, he agrees, but that's of little help to patients who already have cancer. "To prevent something, you have to know its cause. We have no idea why cancer cells spread, let alone what prompts them to disseminate throughout the body."

As in all of cancer research, Welch says, the buzzword in studying metastasis is "heterogeneity." Each patient is different, as are individual tumor cells within a tumor. A tumor cell's behavior is also partly determined by the other cells it interacts with and its proximity to blood vessels for oxygen.

"Tumor cells will always attempt to counteract what the doctors are doing and, like a jilted lover, find ways to not respond," Welch says. "I sometimes compare dormant metastatic cells to terrorist sleeper cells - they remain only a threat as long as they're blending in and not impinging on anything. We need to figure out how to keep them just a threat. But we have a smart enemy."

New department on the block

Welch is hopeful that his new department at KUMC will prove instrumental in finding better ways of pinpointing and reining in metastatic tumor cells. The current faculty of three will welcome their fourth

member in spring 2012. Plans are to eventually recruit five to ten additional faculty and make this department "the go-to place when people think of research possibilities relevant to cancer," Welch says. "I want us to be among the top nationwide in terms of funding, highly collaborative and primed to train the next generation of cancer researchers."

They're headed the right way. Faculty member Animesh Dhar, PhD, was recently awarded the department's first new Research Project (RO1) grant from the NCI to evaluate crocetin, a compound from saffron, as a potential therapy for pancreatic cancer. An application to form a new graduate program is also in the works - a timely initiative, because the Institute of Medicine is considering making cancer biology its own discipline, like biochemistry or pharmacology.

"Cancer biology is involved in the discovery of targets that KU Cancer Center scientists working on prevention or therapy — like the Drug Discovery, Delivery and Experimental Therapeutics program — can then tackle," Welch explains. "Translational research is often thought of as getting therapies into people, which is halfway down the pipe. The new department will focus on the first steps in this pipeline."

Critics of the field have suggested that studying metastasis is as futile as closing the stable door after an escaped horse. But Welch's work leads him to a very different conclusion — it may not be necessary to corral the horse back into the stable, if it can be kept from running amok in the pasture.

"Therapeutically speaking, I see KiSS1 and other suppressors offering a potential compromise where we're able to hold cells that have already spread in a dormant state," he says. "Instead of requiring total elimination of all cancer cells for a cure, metastatic cancer could become a chronic, controllable disease."

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