the Nano-Velcro name. "We can release them simply by changing the temperature," he says. Lowering the temperature changes the polymer's configuration, pulling the antibodies inwards, allowing the tumour cells to detach and flow out of the channel — viable, intact and ready for further study.

LESSONS FROM THE HEART

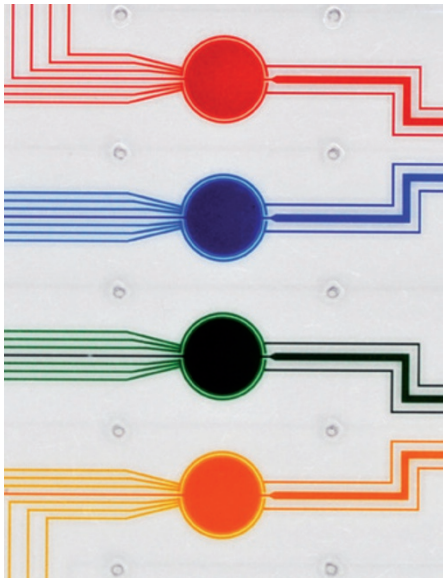
The final stage of metastasis is when the CTCs find fertile 'soil' in the body, to use Paget's term, and begin to grow. It's not clear what makes particular environments hospitable to certain tumour cells, but one place to look for answers is the heart — "the one organ in the body that has actually beaten cancer", according to cardiology researcher Jay Schneider at the University of Texas Southwestern Medical Center in Dallas. Some cancers such as melanoma can metastasize to the heart, but it is "very, very rare", he says. Attempts to achieve metastasis to the heart experimentally have worked only with one cancer cell line, he adds.

The heart's defence mechanism remains unknown, but it seems to be shielded by either mechanical or physical barriers that make the microenvironment hostile to CTCs. It's likely that some component of the heart's microenvironment — maybe its tissue, cells or the scaffolding around the cells — is protecting it. One way to understand the mechanism is to identify what aspect of the 'soil' makes healthy tissue vulnerable to metastatic seeds.

Biomedical engineer Sangeeta Bhatia and her graduate student Nathan Reticker-Flynn at the Massachusetts Institute of Technology (MIT) in Cambridge have built a platform to help them study the interactions between tumour cells and various synthetic models of the ECM (the dense weave of fibrils that make up the scaffolding connecting cells in tissues). The pair want to learn which components of the ECM are most hospitable to metastatic seeds and favour cell migration and adhesion.

Far from being mere stabilizing mortar, the ECM has "its own universe of biology; it is a signalling hub", she says. "And the cells are constantly modifying it, so it's a dynamic and biologically active glue." In a primary tumour, cancer cells stick to one another. To spread, metastatic cells must first detach from their mooring, then move within the ECM to the bloodstream, travel in the blood until they reach a suitable destination, and then attach to the ECM and grow into a tumour there. "The attachment at that metastatic site is what this experiment was about," she says.

Bhatia's team used robots to print arrays of ECM dots, each with a different composition. The researchers scoured catalogues to find all the synthetic ECM molecules on the market and developed 800 unique combinations. They coated glass slides with polyacrylamide, which swells to trap the ECM molecules in one spot, and then seeded metastatic lung cancer cells on the spots. "We developed a platform to query these all at once," Bhatia says, and it has attracted so much interest that she plans to distribute it commercially.



EMD MILLIPORE

This system uses software-based commands to flow cells in a controlled microenvironment.

The researchers imaged the different ways the cells adhered to the ECM spots and compared the adhesion profiles. "We found they have gained the ability to stick to different things than in the primary tumour," she says. As the cells grew over a period of time, the scientists used a clustering algorithm to find patterns in the data. They hope that understanding how tumour cells adhere to the ECM could open the way for a potential therapeutic to interfere with this ability.

THE GAZE OF PHYSICISTS

Metastasis research is benefiting from a multidisciplinary approach that includes biologists, physicists, chemists and engineers. In 2009, for example, the US National Cancer Institute (NCI) started funding a network of 12 Physical Science–Oncology Centers (PSOCs). In 2010 it launched a Provocative Questions initiative requesting research proposals that address "perplexing" problems in cancer, such as devising engineering approaches to improve the study of metastasis.

Another NCI scheme, the Innovative Molecular Analysis Technologies (IMAT) programme, launched in 1998, also fosters these partnerships and aims to develop tools that could accelerate cancer research, says IMAT director Tony Dickherber. "Our understanding of how metastasis works, and the importance and complexity of the microenvironment, is significantly influenced by what tools we have to tell us about either of those things," he says. Several IMAT-funded projects have become widespread research tools as well as commercial products. "I really appreciate the community they have brought together," says Tseng, who received a grant from IMAT.

"We don't prescribe what kinds of innovations we're interested in, we want investigators to come to us and surprise us with their innovative ideas," Dickherber says. The programme puts together interdisciplinary review panels to score prospective research tools according to their potential impact.

Tyler Jacks, who directs the MIT's David H. Koch Institute for Integrative Cancer Research, says his institute is "expressly about bringing biologists and engineers together under one roof". Collaborations are encouraged by ensuring that everyone circulates in the same sections. "We're neighbours now and we interact much more extensively," he says.

Physicist Jean-François Joanny at the Curie Institute in Paris is also using his expertise to benefit cancer biology. Building on work by the late Malcolm Steinberg, a Princeton University biologist, Joanny's team has looked at how pressure affects the growth of clusters of cancer cells known as spheroids. Perhaps a physical property is what distinguishes cancer cells. "Could you characterize the degree of invasiveness by looking at properties like this?" he says. "That's the idea at the back of our minds."

One cancer biologist proposed a scientific challenge for Joanny's group. He asked the physicists to make pressure measurements in a mouse with multiple tumours and determine, from those measurements alone, which cancer is most likely to metastasize. As the biologist knows the correct answer, his team will use biology to validate the physics-based results.

The Curie Institute has a tradition of cross-disciplinary collaboration, with cancer biologists approaching suggestions from physicists with open minds, Joanny says. "We are used to the idea that they might consider us crazy." But if wild ideas from physicists can boost the fight against cancer — and their work to help biologists understand the various processes of metastasis suggests that they can — then maybe they're not quite so crazy after all. ■

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CORRECTION

The Technology Feature 'Two microscopes are better than one' (*Nature* **492,** 293–297; 2012) wrongly stated that the enzyme APEX is a singlet oxygen generator, it is a peroxidase. Also, Alice Ting was a postdoc in the lab of Roger Tsien, not Mark Ellisman.