

## How to stop cancer from spreading

Breast cancer kept from the lungs of mice with simple drug cocktail.

Helen Pearson

Breast cancer has been prevented from spreading in mice with a simple cocktail of drugs, some of which are already approved for human use.

The spread, or metastasis, of cancer is the most dreaded aspect of the disease: tumours formed this way are responsible for 90% of cancer deaths. But the process has been difficult to fathom — two tumours may by all appearances be identical, yet one will spread and one will not. And a tumour may shed hundreds or thousands of cells into the bloodstream every day, of which only a tiny fraction will successfully lodge in a new site and start to proliferate into a new cancer.

In 2005, Joan Massagué at the Memorial Sloan-Kettering Cancer Center in New York identified a roster of genes that seem to help breast cancer cells to metastasize to the lung<sup>1</sup>. Now Massagué's team has shown how four of these genes specifically work in concert to fuel metastasis. Addressing these four genes with drugs, they show in mice, has a dramatic effect.

Massagué hopes that this approach will work better than existing treatments, because it is targeted against genes now proven to fuel tumour growth and metastasis. And, he notes, two of the drugs are already in clinical use, which should speed clinical trials. "You couldn't have it better," he says. Other researchers say they would like to see data from human patients before getting too excited.

### Four together

The researchers proved the action of the four genes by silencing them in a line of human breast cancer cells, before injecting them into mice. The gene silencing halted the growth of breast tumours in the mice, and almost completely blocked the formation of lung metastases, they report in Nature<sup>2</sup>. Silencing only one of the genes at a time, by contrast, had far less effect.

The team propose that the four genes (called EREG, MMP1, MMP2 and COX2) are vital both for aggressive growth of the primary tumour and for metastasis: they help to hijack a network of blood vessels to nourish the tumour's own growth, help tumour cells escape into these same blood vessels to reach the lung, and help them to weasel their way through the capillary wall, set up shop and grow.

The researchers showed that a combination of existing drugs known to inhibit the genes' action — two approved drugs called cetuximab and celecoxib, plus an experimental one called GM6001 — had a similar effect to silencing the genes. The two approved drugs on their own also served to stop the cancer spread.

Massagué says the next step is to find women whose breast tumours are relying on these four genes, and to test whether this combination of drugs would help to protect them from lung cancer. He is now working with doctors to initiate clinical trials.

### Born to kill

The study challenges a long-standing idea that the tendency to metastasize is picked up late in a tumour's life. Massagué's results support an alternative hypothesis, that certain tumour cells possess the ability to metastasize from the outset — and in this case, the same genes that drive the growth of the primary tumour are the ones that drive the cells to metastasize.

Researchers don't yet know whether these four genes are also involved in the metastasis of other cancer types. There are now thought to be hundreds of different cancer types and it is conceivable that each uses slightly different ploys for growing and spreading. That would make it much harder to treat. "I hope there are rules," says Christoph Klein, who studies metastasis at the University of Regensburg, Germany.

There are many other aspects of metastasis that remain mysterious. Some patients turn up at the doctor with metastases even though, mysteriously, their primary tumour is never found. And little is known about why particular cancers show a proclivity for spreading to particular tissues, such as breast cancer's particular preference to target bone and lung.

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Targetting four genes with drugs can stop at least one type of breast cancer from spreading in mice.

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### References

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2. Gupta G. P., *et al.* Nature, 446 . 765 - 770 (2007). | [Article](#) | [PubMed](#) | [ChemPort](#) |