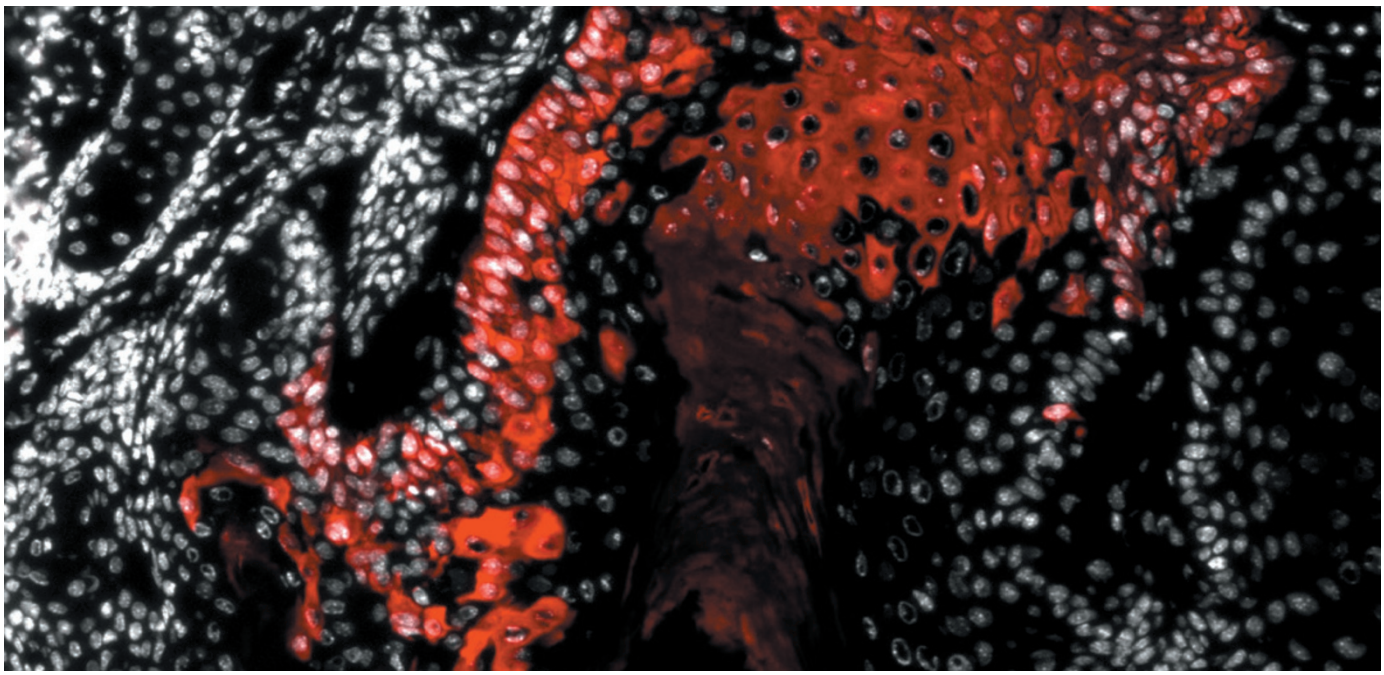
NEWS IN FOCUS

G. DRIESSENS



For the first time, researchers can trace cell lineage within a growing tumour. In this skin tumour, the cells labelled red all arose from a single stem cell.

ONCOLOGY

Cancer stem cells tracked

The master builders that underlie tumour growth may inform treatment strategies.

BY MONYA BAKER

Cancer researchers can sequence tumour cells' genomes, scan them for strange gene activity, profile their contents for telltale proteins and study their growth in laboratory dishes. What they have not been able to do is track errant cells doing what is more relevant to patients: forming tumours. Now three groups studying tumours in mice have done exactly that[1–3]. Their results support the ideas that a small subset of cells drives tumour growth and that curing cancer may require those cells to be eliminated.

It is too soon to know whether these results — obtained for tumours of the brain, the gut and the skin — will apply to other cancers, says Luis Parada at the University of Texas Southwestern Medical Center in Dallas, who led the brain study[2]. But if they do, he says, "there is going to be a paradigm shift in the way that chemotherapy efficacy is evaluated and how therapeutics are developed". Instead of testing whether a therapy shrinks a tumour, for instance, researchers would assess whether it kills the right sorts of cell.

Underlying this scenario is the compelling but controversial hypothesis that many tumours are fuelled by 'cancer stem cells' that produce the other types of cancer cell, just as ordinary stem cells produce normal tissues. Previous studies have tested this idea by sorting cells from a cancer biopsy into subsets on the basis of factors such as cell-surface markers, and injecting them into laboratory mice. In principle, those cells that generate new tumours are the cancer stem cells. But sceptics point out that transplantation removes cells from their natural environment and may change their behaviour. "You can see what a cell can do, but not what cells actually do," says Cédric Blanpain of the Free University of Brussels, who co-led the skin study[1].

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All three research groups tried to address this knowledge gap by using genetic techniques to track cells. Parada and his co-workers began by testing whether a genetic marker that labels healthy adult neural stem cells but not their more specialized descendents might also label cancer stem cells in glioblastoma, a type of brain cancer. When they did so, they found that all tumours contained at least a few labelled cells — presumably stem cells. Tumours also contained many unlabelled cells[2]. The unlabelled cells could be killed with standard chemotherapy, but the tumours quickly returned. Further experiments showed that the unlabelled cells originated from ▶

labelled predecessors. When chemotherapy was paired with a genetic trick to suppress the labelled cells, Parada says, the tumours shrank back into "residual vestiges" that did not resemble glioblastoma.

Meanwhile, Hans Clevers, a stem-cell biologist at the Hubrecht Institute in Utrecht, the Netherlands, and his colleagues focused on the gut. They had previously shown that a genetic marker that labels healthy gut stem cells also labels stem cells in benign intestinal tumours, which are precursors of cancer[4]. In their latest study[3], he and his team engineered mice to carry a gene for a drug-inducible marker that, when activated, causes labelled cells to make molecules that fluoresce one of four colours. This experiment yielded single-colour tumours consisting of several cell types, suggesting that each tumour arose from a single stem cell. To check that stem cells continued to fuel the tumours, Clevers added a second, low dose of the drug, triggering a few of the stem cells to change colour. This produced streams of cells in the new colour, showing that stem cells were consistently producing the other cell types.

For the skin study, Blanpain and his group labelled individual tumour cells, without targeting stem cells specifically[1]. They found that cells showed two distinct patterns of division: they either produced a handful of cells before petering out, or went on to produce many cells. Once again, the results pointed to a distinct subset of cells as the engine of tumour growth. What's more, as tumours became more aggressive, they were more likely to produce new stem cells — which can divide indefinitely — and less likely to produce differentiated cells, which can divide only a limited number of times. That could be a key to halting tumour development early, says Blanpain. Rather than eradicating cancer stem cells, for example, therapies could try to coax them to differentiate into non-dividing cells.

The papers provide clear experimental evidence that cancer stem cells exist, says Robert Weinberg, a cancer researcher at the Whitehead Institute in Cambridge, Massachusetts. "They have made a major contribution to validating the concept of cancer stem cells," he says. But cancer cells probably also act in more complex ways than those observed, he warns. For example, non-stem cells within the tumour might de-differentiate into stem cells.

The next step, the three groups say, is figuring out how the cells tracked in these experiments relate to putative cancer stem cells identified by years of transplantation studies. Researchers are already busy hunting for ways to kill these cells; now they have more tools to tell whether such a strategy will work. ■

1. Driessens, G., Beck, B., Caauwe, A., Simons, B. D. & Blanpain, C. *Nature* http://dx.doi.org/10.1038/nature11344 (2012).
2. Chen, J. *et al. Nature* http://dx.doi.org/10.1038/nature11287 (2012).
3. Schepers, A. G. *Science* http://dx.doi.org/10.1126/science.1224676 (2012).
4. Barker, N. *et al. Nature* **457,** 608–611 (2009).

THERAPEUTICS

FDA's claims over stem cells upheld

Drug watchdog wins right to regulate controversial therapies.

BY DAVID CYRANOSKI

A court decision on 23 July could help to tame the largely unregulated field of adult stem-cell treatments. The US District Court in Washington DC affirmed the right of the Food and Drug Administration (FDA) to regulate therapies made from a patient's own processed stem cells. The case hinged on whether the court agreed with the FDA that such stem cells are drugs.

The judge concurred, upholding an injunction brought by the FDA against Regenerative Sciences, based in Broomfield, Colorado. Under the treatment sold by the firm, stem cells are isolated from patients' bone marrow, processed, and the resulting cells injected back into the patients to treat joint pain. The FDA calls this procedure the "manufacturing, holding for sale, and distribution of an unapproved biological drug product", and in August 2010, ordered Regenerative Sciences to stop offering the treatment (see *Nature* **466,** 909; 2010).

"Maintaining the FDA's role as watchdog and regulatory authority is imperative."

During investigations leading up to the injunction, the FDA also found that, because of flaws in its cell processing, the company was violating regulations on "adulteration" that are meant to ensure patients' safety.

Jeanne Loring, a regenerative-medicine scientist at the Scripps Research Institute in La Jolla, California, says that the decision will send a warning to other entrepreneurs offering unapproved stem-cell treatments. "So many people want to start these companies. They say, 'FDA? What FDA?'."

Chris Centeno, the medical director of Regenerative Sciences and one of two majority shareholders, told *Nature* that he plans to appeal against the ruling. During the case, the company claimed that the cells in its 'Regenexx' procedure are not significantly modified before they are reinjected, so the procedure should be considered routine medical practice. The company also argued that because all the processing work is done in Colorado, the procedure should be subject to state law, rather than to regulation by the FDA.

The court disagreed on both counts, noting that "the biological characteristics of the cells change during the process", and that this, together with other factors, means the cells are more than "minimally manipulated".

Leigh Turner, a bioethicist at the University of Minnesota in Minneapolis, agrees. "It is much too simplistic to think that stem cells are removed from the body and then returned to the body without a 'manufacturing process' that includes risk of transmission of communicable diseases," he says. "Maintaining the FDA's role as watchdog and regulatory authority is imperative."

Centeno says that the FDA injunction applies to only one of his company's four stem-cell products — one that requires 4–6 weeks of processing. The procedure will still be available: after the 2010 injunction, the company moved its treatment location to an affiliated Cayman Island clinic.

Centeno plans to continue providing the other three procedures, also used for joint pain, in the United States. In those treatments, the cells are reinjected within two days. Centeno claims that those cells are "minimally manipulated", and that the FDA sees them as the "practice of medicine" and "has no issues" with them. Indeed, until 25 July, a graphic on the Regenerative Sciences website claimed that these three procedures were "FDA approved".

In fact, the FDA has not approved these procedures, and Centeno did not provide documentation to support his claims that the agency views the three treatments as outside its purview. The graphic was removed after *Nature*'s enquiries.

Doug Sipp, a stem-cell ethics and regulation expert at the RIKEN Centre for Developmental Biology in Kobe, Japan, worries that more stem-cell companies might now set up shop outside the United States to avoid regulation, as Regenerative Sciences has done. "Other US stem-cell outfits have close ties with partner clinics in Mexico and other neighbouring countries, which are traditionally regulatory havens for other forms of fringe medicine as well. I suppose it will be business as usual in such places," Sipp says. ■