

The root of the problem

Is targeting cancer stem cells a way to finish tumours off once and for all — or just the latest in a long line of false dawns? **Alison Abbott** looks at a debate that's generating both heat and light.

"Your cancer has returned." The words that patients most dread are the ones that most of them eventually hear. Why tumours that had been shrunk to nothing by a first round of treatment should recur has long been a mystery. Now, a growing number of researchers think it may be because biologists have overlooked a key part of how cancers grow.

It's all down to stem cells, they say. Normal stem cells repair and renew our tissues. Recently, research has focused on the idea that a kind of evil twin, a cancer stem cell, could stock a tumour with cancer cells, rather like the way a weed can grow back from its roots. If the idea is right, then cancers return because existing treatments cut down the leaves and shoots but leave the roots intact.

According to the theory, cancer stem cells have a physiology that makes them particularly resistant to typical treatments. They lurk for months or years, then re-seed the cancer, usually in a more aggressive, often fatal, form (see 'Why the drugs don't work'). Find a treatment that targets the cancer stem cell, without harming normal stem cells — as researchers are already trying to do — and scientists might be able to protect against recurrence.

It's a controversial idea. The theory is promising, but the field is awash with hype. Researchers observe wryly that more reviews seem to have been published than primary papers. Ideas abound about how the theory explains every aspect of cancer, and about where and how to find therapeutic targets. Hard data are emerging only slowly.

Sean Morrison, a stem-cell biologist at the University of Michigan, Ann Arbor, who reported one of the first key differences between normal and cancer stem cells in May¹ remains downbeat. "Remember apoptosis, remember angiogenesis?" he asks rhetorically. These properties of cancers — respectively, their ability to bypass the normal cell-suicide response to damage, and their ability to create their own blood supply — were once seen as routes to powerful therapies, but have yet to live up to their initial promise.

Yet whatever their clinical potential, the idea of cancer stem cells is prompting biologists to think about cancer in a new way.

Many different tissues harbour adult stem cells. The cells don't normally divide much, but when prompted by death in their realms, they

do so asymmetrically.

One of the two daughter cells is a replica of the parent cell — the property of self-renewal — and the other is a 'progenitor' cell that goes on to differentiate into more specialized cells. Neural stem cells, for example, can replace both of the brain's major cell types, neurons and glia. Blood stem cells can replace myriad red and white blood cells.

Cancer stem cells share the ability to self-renew and to spawn many different kinds of cell. They were identified in leukaemias in the late 1990s. John Dick at the University of Toronto harvested leukaemic cells from patients and found that only a small proportion could reproduce the same cancer in immune-deficient mice². The ability to recapitulate the same cancer is what defines a cancer stem cell.

In the blood

Leukaemia is relatively easy to work with. You can access the cancer cells by drawing blood, and blood stem cells are well-characterized, particularly in terms of the presence or absence of specific marker proteins that define 'stemness'. Getting hold of fresh a solid tumour is more difficult, and much less is known about the relevant markers. That said, cancer stem cells have now also been demonstrated in breast³ and brain⁴ tumours. They bear convincing markers of stemness, and they can recapitulate the cancer.

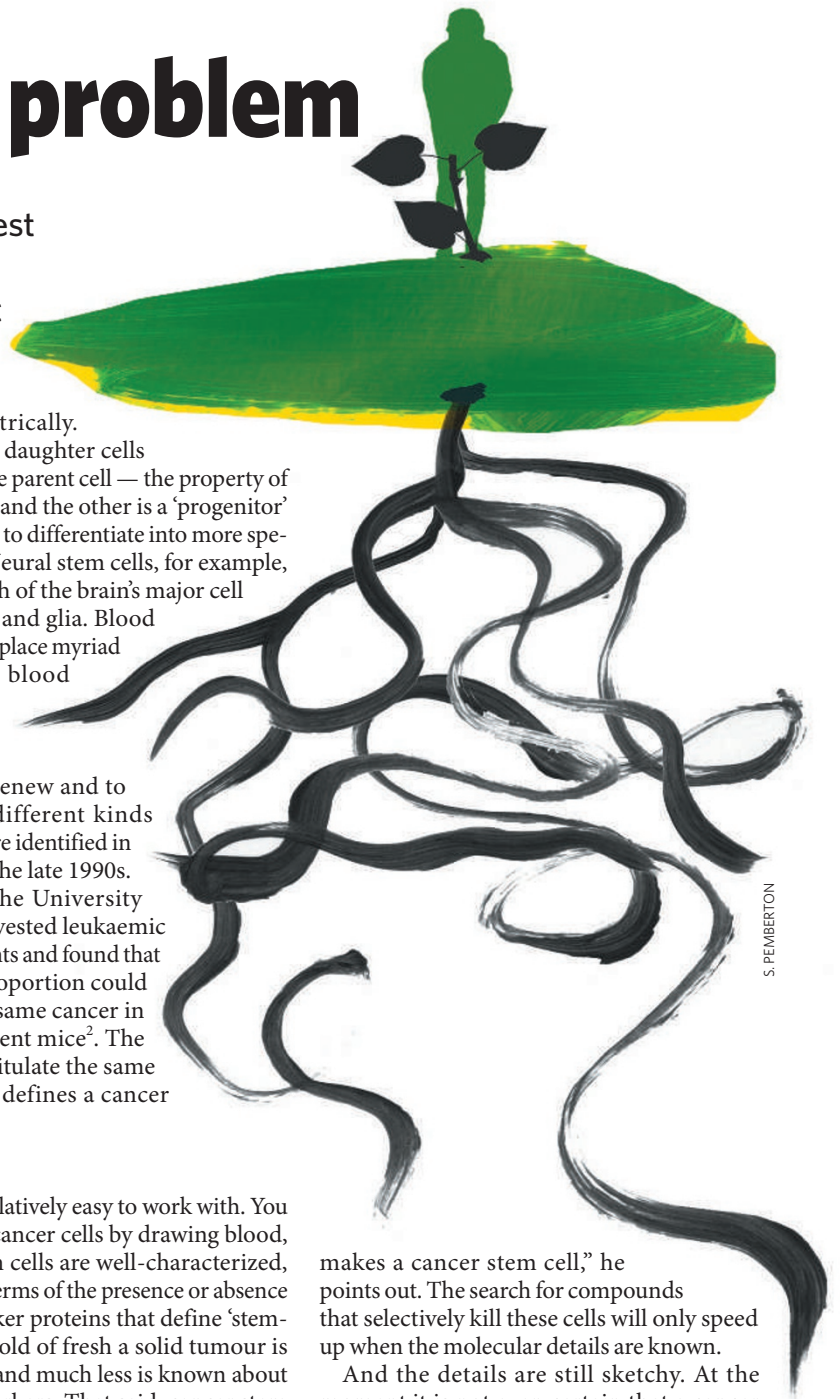
There are also many early reports of stem-like cancer cells in other solid tumours such as ovarian, lung and skin cancers that have yet to meet all the criteria of proof. "There is no question in my mind that cancer stem cells will prove to be the rule rather than the exception," says Michael Clarke, of the Stanford Comprehensive Cancer Center. It's just a question of time to get the results, he thinks.

On the other hand, oncologist William Hahn of Harvard University — who describes himself as "a sceptical observer who likes the idea of cancer stem cells" — is more circumspect. "There is no real molecular definition of what

makes a cancer stem cell," he points out. The search for compounds that selectively kill these cells will only speed up when the molecular details are known.

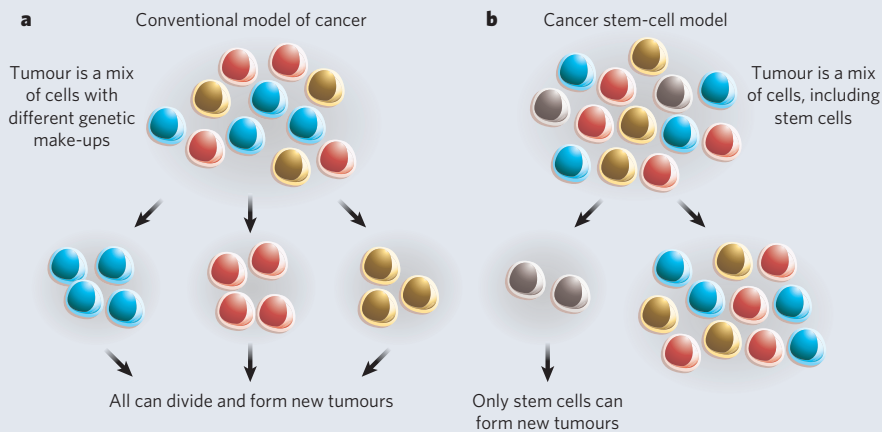
And the details are still sketchy. At the moment it is not even certain that a cancer stem cell derives directly from a normal stem cell, although this will probably often be the case. Cells become cancerous when they have accrued a critical number of mutations in genes in the interacting signalling pathways that control growth, allowing the cells to evade the normal mechanisms that restrict growth. Unlike many cells, stem cells live long enough to acquire the required changes.

But researchers have shown that a non-stem cell that picks up a mutation giving it the ability to self-renew might also develop into a cancer stem cell⁵. Different cancers probably contain cancer stem cells of different origin. But the origin of cancer-initiating cells is less important to those seeking therapeutic targets than finding molecules in them that they do not share with tissue stem cells.



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WHY THE DRUGS DON'T WORK



Current cancer therapies target the main body of tumour cells, once thought to be the source of cells that seed new tumours (a). But a new theory (b) suggests that only a subset of tumour cells, cancer stem cells, can do so. These have markedly different properties and might need to be targeted to prevent tumour recurrence.

Given that so little is known about marker molecules in any sort of stem cell, at the moment it's a bit like trying to do a crossword without all the clues. But a couple of groups have identified two molecular signalling pathways that are regulated differently in the two stem-cell types. And these present the first leads for potential therapies targeting cancer stem cells.

Flower power

Craig Jordan, a molecular biologist at the University of Rochester, New York, has identified a molecular signalling system that is permanently switched on in leukaemia stem cells but not in blood stem cells. He found that the molecule parthenolide, the main active ingredient in feverfew, a herbal medicine used to treat migraines, blocks a key component of this system. This prompts leukaemic stem cells to commit suicide, whereas normal stem cells are unaffected⁶. Jordan says he hopes to have a derivative of the molecule in clinical trials by the end of the year.

Morrison's discovery was that deleting a gene called *Pten*, commonly inactivated in human leukaemia, stimulates the growth of leukaemia stem cells but inhibits the growth of normal blood stem cells. And he found that the drug rapamycin reversed the effect of the gene deletion in mice, leaving the cancer stem cells unstimulated, and reactivating the growth of blood stem cells¹. Rapamycin is used clinically as an immunosuppressant to prevent transplanted organs being rejected, and several variants happen to be in clinical trial for cancers. His group's findings are sure to affect how the trial results are interpreted, says Morrison.

Other pathways that are often aberrantly activated in cancer may or may not be differently regulated in normal

and cancer cells. These pathways have been pillars of mainstream cancer research for years, and are now acquiring a stem-cell spin. Two of the many contenders are the *Wnt* and *Sonic hedgehog* pathways which, in their healthy manifestations, play a key role in embryonic development, stem-cell renewal and tissue repair.

"There is no proof that *Sonic hedgehog* is involved in cancer stem cells but my intuition is that it will be," says molecular biologist Michael Dean of the National Cancer Institute in Frederick, Maryland. He is already looking for candidate drugs, initially using cyclopamine, a molecule found in the poisonous lily *Veratrum californicum*. Cyclopamine interrupts *Sonic hedgehog* signalling in prostate, gut and brain cancers.

The hard core of cancer-stem-cell researchers view this tendency to hang a new collar on an old dog with caution. "There are a lot of hypotheses, but you have first to distinguish

"Some of the pillars of mainstream cancer research are getting a stem-cell spin."

between stem cells that generate tumours and those that do not," says Morrison.

Also getting a cancer stem-cell spin are the 'drug pumps'. These membrane proteins, which have long been therapeutic targets, remove drugs and other foreign molecules from a cell. They are believed to be a major cause of the resistance that cancer cells develop to drugs that initially shrink tumours.

Resistance cell

Stem cells are assumed to be built like fortresses, with multiple mechanisms to protect them from toxic environmental agents, so they don't replace tissue with damaged goods. Cancer stem cells might also be packed with drug pumps, explaining their presumed extreme resistance to therapies. Some suspect the unexpected occurrence of resistance to Gleevec — the first anticancer agent targeted to a specific signalling-pathway component, called BCR-ABL — could be down to cancer stem cells' ability to pump the drug out. Dean, for example, is screening compounds in the hope of targeting such drug pumps in cancer stem cells.

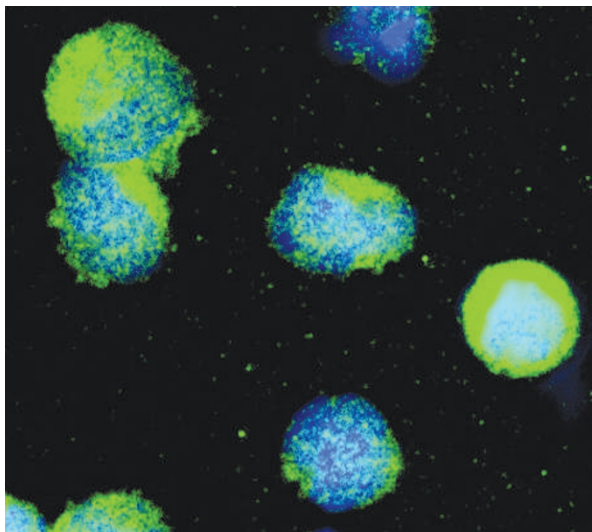
A different approach to hitting cancer stem cells is to make highly specific antibodies that can seek out and kill them. This requires a deep understanding of the proteins found only in cancer stem cells, which antibodies could target. It seems a tall order, but a number of

biotech companies are trying to develop such methods.

Outside the search for therapeutic targets, established themes of cancer are also being recast in the light of the stem-cell concept. Could it for example, give insights into metastasis, given that normal stem cells can relocate to repair distant tissue? Could it explain why chronic injury frequently results in cancer, as in such circumstances stem cells are called upon to continuously replace tissue and thus increase their chances of acquiring mutations?

Even those scientists who fear that the cancer stem cell may prove to be a sidetrack don't believe it will be a dead-end — simply because such a lot of cancer biology is being reconsidered, and new things uncovered, en route. And if the concept performs beyond expectation, then the root-killing generation of therapeutics will emerge to ensure permanent remissions, to protect patients from deadly cancer recurrence. ■

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Leukaemia stem cells have the ability to seed new cancers.

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